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LEGAL MEDICINE AND TOXICOLOGY

BY MANY SPECIALISTS

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GENERAL PRINCIPLES OF TOXICOLOGY

BY WALTER S. HAINES, M. D.

CHICAGO

Definition.—Toxicology is the science that treats of poisons, their origin, properties, and action on the system, the treatment of their noxious effects, and their detection by chemical or other means.

Up to comparatively recent years the science of toxicology embraced in its domain only poisons of well-defined character, coming chiefly from the mineral and vegetable kingdoms, such as arsenic, strychnin, and morphin. Within a relatively short time, however, it has been discovered that a large number of diseases are produced by the action of certain poisonous substances generated within the system either by the normal cells of the body or by micro-organisms. These compounds, known according to their origin and properties as leukomains, ptomains, toxins, etc., properly come within the scope of toxicology and give to the science a greatly increased field. It naturally is not customary, however, to deal with these substances in works like the present on forensic toxicology, but rather to leave their discussion to books on pathology and the practice of medicine, or to treatises devoted especially to them.

It is a difficult matter to give an exact definition of the term "poison." This arises from the fact that it is impossible to set aside any group of substances that are poisons under all conditions; a body may be entirely harmless under certain circumstances, and yet under others be possessed of dangerously poisonous properties. The salts of potassium, for example, in small quantity are not only not poisonous, but are necessary for the maintenance of a healthy condition of the body; in large doses, however, they are active poisons, capable with great certainty of producing death. Most medicines if administered in too large quantity become poisons; and conversely, nearly, if not quite all, poisons, if given in small doses, are possessed of remedial properties. The line, in fact, between a medicine and a poison is often exceedingly narrow. No substance is known that is a poison in all doses; a certain amount, varying, however, very widely with different bodies, is necessary in order that poisonous effects may follow its administration.

Herter's¹ view, that there is no soluble substance known that does not possess toxic properties when given in sufficiently large quantity, is unquestionably true; and Rowntree and associates have shown experimentally that even pure water administered in excessive amount produces violent poisoning and death.²

¹ C. A. Herter, *The Action of Sodium Benzoate and Benzoic Acid on the Human Organism*, Baltimore, 1910, p. 18.

² *Jour. Amer. Med. Assoc.*, June 10, 1922, p. 1840.

The definition given by Taylor¹ is, when slightly modified, perhaps as comprehensive and as scientific as any:

A poison is a substance which, when absorbed into the blood, is capable of seriously affecting health or of destroying life, and this is its usual effect upon the healthy body.

It will be observed from the above—

First, that a poison is a material substance, and not an imponderable agency, such as electricity or heat.

Second, that it is a body which acts after absorption into the blood, and does not produce its effects, therefore, by mere mechanical action. Pounded glass, needles, and other similar articles, although capable of producing death when taken in sufficient quantity, act mechanically only, and are not poisons in the true sense of the word. For similar reasons, it may be a question whether the corrosive acids and alkalis should be considered as poisons. Their chief effect is a local one and is produced without absorption into the blood, and on this account some writers² on toxicology do not embrace them under the strict head of poisons. Since, however, in nearly all cases a certain part of the corrosive agent enters the circulation and produces harmful systemic effects, their exclusion from the category of poisons seems, on the whole, unnecessary, and for many practical reasons undesirable.

Third, that a substance which produces noxious effects as an unusual result, or by acting upon a diseased body, is not necessarily a poison. Many ordinary articles of food, as is well known, are occasionally the cause of distressing and sometimes even of serious symptoms when taken by people who have an idiosyncrasy to them. Strawberries cannot be eaten by a considerable number of people without unpleasant effects,³ and the writer is acquainted with a gentleman in robust health who is made exceedingly ill not only by eating apples, but even by their odor. Strawberries and apples, however, manifestly should not come within the definition of a poison; nor do they, as the term is defined above, as the noxious results noted are not their *usual* effects. And similarly, improper articles of food, which have more than once produced fatal effects with typhoid patients, are equally excluded by our definition from the category of poisons.

Fourth, that whether a substance is a poison or not is in no way dependent on the quantity that must be used to produce noxious results. Half a grain of strychnin may produce death, while 60 grains of oxalic acid are required to occasion fatal results.

Although from a strictly scientific standpoint the size of dose necessary to produce noxious effects has nothing to do with the conception of a poison, yet, as commonly understood and as generally accepted in ordinary life, the term "poison" is closely connected with the amount required to induce serious results. Common salt in large

¹ On Poisons, 3d ed., 1875, p. 18.

² Witthaus and Becker, Medical Jurisprudence, Forensic Medicine, and Toxicology, 1911, iv, p. 51.

³ Gould and Pyle, Anomalies and Curiosities of Medicine, p. 489, where several cases of illness and one of death from the eating of strawberries are cited.

doses is capable of producing noxious effects, and has even occasioned death,¹ but it is not commonly looked upon or spoken of as a poison, the quantity required for these results being so large. In a recent case of forensic importance, a group of experts, after consultation, agreed on the following definition of a poison to cover the general acceptance of the term as used in everyday life: *A poison is a substance, which, when introduced into the body in relatively small quantity and acting chemically, is capable of producing death or serious injury to health in the case of an ordinary individual in average health.* This definition would seem to be an extremely acceptable one, as it includes the important points of the action of the poison on an ordinary individual in average health, thus ruling out the occasional cases of untoward action of drugs on persons showing idiosyncrasies to such drugs and, also, those cases of injurious effects on persons in failing health.

In order to avoid any uncertainty as to the inclusion of the corrosives and the mechanical irritants, the statutes commonly speak of "the administration of a poison or of other noxious or destructive thing," or use other words to the same effect. Legal quibbling in regard to definitions is thus eliminated or reduced to a minimum.

Classification of Poisons.—A large number of classifications of poisons have been suggested, but none of them is entirely satisfactory. Two general systems of classification have usually been adopted, the first depending upon the origin or nature of the substance; the second, upon the effect it produces on the system.

Were our knowledge of the actions of poisons absolutely definite, the second system of classification would unquestionably be the most desirable; but since, in the present state of science, our information on this point is by no means complete, any close classification made upon this line is necessarily faulty. A simple, general division of poisons, however, into **corrosives**, **irritants**, and **neurotics**, according as the chief effect produced is local corrosion, gastro-intestinal irritation, or altered action of the nervous system, is often exceedingly useful, and is the one I prefer if the classification is based on the effects shown. In this classification under *corrosives* are included the strong acids and alkalis, whose most important action is local destruction of the tissues; under *irritants*, those numerous substances, such as arsenic, antimony, mercury, and most of the other heavy metals, phosphorus, bromin, iodin, and a certain number of organic substances like cantharides, savin, and croton oil, whose most conspicuous effects are usually gastro-intestinal irritation, as shown chiefly by vomiting, purging, and local pain; and under *neurotics*, the majority of organic poisons, prominent among which are alcohol, chloral, chloroform, opium, belladonna, aconite, strychnin, acetanilid, carbon monoxid, hydrocyanic acid, and phenol (carbolic acid), all of which expend their toxic powers chiefly on the nervous system, producing delirium, coma, convulsions, and disordered circulation and respiration as prominent symptoms.

¹ Medical Times, January 4, 1840, p. 133 (referred to in Woodman and Tidy's Forensic Medicine and Toxicology); American Medicine, April 22, 1905, p. 640.

Even this division, however, is seriously deficient and far from satisfactory, as very many poisons act in two or more different ways: oxalic acid in concentrated solution is a corrosive, in dilute solution an irritant, and in either case it also acts powerfully on the nervous system, and the same may be said of mercuric chlorid, phenol (carbolic acid), and numerous other poisons.

As an interesting contribution to this system of classification we give below the grouping of poisons suggested by Rabuteau.¹ It is very faulty, as modern pharmacologic investigation has shown and as any classification on this line must necessarily be in the present state of our knowledge, but is suggestive of what may finally be done in this direction when further research has more fully informed us of the exact mode of action of our various poisons.

I. HEMATICS.

- 1st. Those acting specially on the red corpuscles: Carbon monoxid, hydrocyanic acid, hydrogen sulphid and ammonium sulphid, phosphorus, the alcohols, and the compounds of arsenic, selenium, and tellurium.
- 2d. Those acting on the corpuscles and the plasma: Nitrites and nitrous vapors, salts of silver injected into the veins, the majority of metallic salts (in small and continued doses).

II. NEUROTICS.

- 1st. Motor paralyzers, abolishing the functions of the motor nerves: Curara, Calabar bean, aconitin, and coniin.
- 2d. Spinants, exaggerating reflex action: Strychnin, akazga, compressed oxygen, cantharides, etc.
- 3d. Cerebrospinants, acting on the brain and spinal cord: Chloroform, ether, and opium.

III. NEUROMUSCULAR.

Solanaceæ, digitalis, and compounds of antimony.

IV. MUSCULAR.

Carbon dioxid, strophanthus, veratrin, and salts of potassium, barium, copper, zinc, cadmium, tin, lead, mercury, etc.

V. IRRITANTS AND CORROSIVES.

Sulphuric, nitric, hydrochloric, hydrofluoric, oxalic acids, potassium and sodium hydroxids, ammonia, alkaline sulphids, iodine, bromine, chlorine, etc.

After mature consideration of the subject I finally agree fully with Chapuis,² that under present conditions the most useful classification of poisons for forensic purposes is that depending on their origin or nature, and consequently, in the present book, the division adopted is the following: First, Inorganic Poisons; Second, Gaseous Poisons; Third, Alkaloidal Poisons; Fourth, Non-alkaloidal Organic Poisons; and Fifth, Food-poisons. This classification commits us to no theory regarding the precise action of a poison, and at the same time it brings together those of a similar nature from an analytic standpoint and possessed otherwise of many points in common—items of much moment in forensic toxicology to all concerned.

¹ *Éléments de toxicologie*, 1873, p. 31.

² *Précis de toxicologie*, 3d ed., 1897, p. 119.

CONDITIONS AFFECTING THE ACTION OF POISONS

The effects of poisons on the system are often very materially modified by a number of circumstances, and these may be conveniently divided into two groups: I. Those relating to the poison itself and its administration; and II. Those relating to the individual.

I. Under the first heading we have two chief subdivisions: 1. The form of the poison; and (2) the avenue of its entrance into the circulation.

1. **Form of the Poison.**—We have seen that, in order that a substance may act as a poison, it must be capable of entering the blood; in other words, it must be a soluble body. It is evident, therefore, that no substance can be a poison that is entirely insoluble. Other things being equal, a given poison is more active the more soluble the form in which it is administered; barium, for instance, when combined with chlorin, as the readily soluble chlorid, is highly poisonous, but when united with sulphuric acid, as the insoluble sulphate, it is destitute of toxicity.* This general principle is extensively taken advantage of in antidoting poisons, as will be seen later.

Poisons in the form of a solid generally produce their effects more slowly and less energetically than when taken in solution; in pills and capsules their action is likely to be particularly retarded. In these latter forms they may pass through the intestinal tract incompletely or irregularly dissolved, and possibly occasion, therefore, unexpected results. The case cited on page 26, in which the symptoms of arsenic poisoning did not appear until the sixteenth hour, undoubtedly owed the long delay chiefly to the fact that the poison was taken in the form of a dry powder and without fluid to wash it down. Pashley¹ relates a remarkable case in which a healthy young man swallowed in pills 3 grains of strychnin, a dram of opium, and a considerable quantity of quinin, and no characteristic effects were developed until twelve hours had elapsed; coma then supervened and the man died a number of hours later, without, however, at any time showing symptoms indicating the action of strychnin.

In this connection it may be stated that poisons when taken on a stomach full of solid food are generally more slowly dissolved and less rapidly absorbed, and, as a consequence, produce their effects somewhat more tardily and frequently less severely than if taken when the stomach is empty or contains but little food. The importance of this fact in forensic toxicology is often great, as it explains at times many seeming anomalies in the action of poisons.

Dilution of a poison by water to a certain extent, by favoring its more rapid absorption, usually hastens and intensifies its action. Corrosive poisons, however, as would be expected from their very nature, have their activity greatly diminished by dilution.

2. **Avenue of Entrance Into the Circulation.**—As a rule, poisons produce practically the same effect by whatever path they enter the blood, the only difference being due to the different rates of absorp-

¹ Chicago Med. Jour., November, 1860, iii (n. s.), p. 625.

tion. Administration by inhalation, by hypodermic injection, or by direct injection into the blood-current causes generally much more rapid and energetic symptoms than when the poison is given by the stomach or rectum; but otherwise the effects are usually identical or not greatly different. In a few cases, however, the avenue of entrance materially modifies the action. Thus, snake-poisons when given by the mouth are entirely harmless; and curara is toxic in only a very slight degree when administered by the stomach, although intensely poisonous if given hypodermically. Hydrogen sulphid, even in small amount, is extremely poisonous when inhaled into the lungs, but the same quantity may be administered by the rectum, or, when in solution, by the mouth, without danger. Chloroform, ether, and a number of other analogous substances occasion effects quite different in some respects when administered by the mouth from those produced when given by inhalation.

The experiments of Kolmer¹ on animals strikingly show the great difference in the quantitative effects of poisonous drugs according to the route of administration.

II. The chief conditions relating to the individual that modify the effect of poisons are: 1, Age; 2, Idiosyncrasy; 3, Habit; 4, Tolerance; 5, Disease.

1. **Age.**—As would naturally be inferred, the age of a person decidedly affects the susceptibility to poisons. The general rule is that the younger the person, the greater the susceptibility. There are, however, some exceptions to this, young children, for example, being far more tolerant of calomel and belladonna than adults. But, on the other hand, certain poisons act upon infants with unexpected severity; and this is especially true of opium and its preparations, and of narcotic drugs in general, all of which are much more poisonous proportionally to young children than to the adult. One or two drops of laudanum have proved fatal to infants, and Taylor² relates a case in which an infant four weeks of age died presumably from the effects of a quantity of paregoric equivalent to only $\frac{1}{90}$ grain of opium.

2. **Idiosyncrasy.**—Many persons manifest an unusual, and in most cases inexplicable, sensitiveness to the action of certain poisons, and this fact has not infrequently been the cause of serious disturbance, and even of death, from the remedial administration of these substances in the practice of medicine. Marked individual intolerance of antipyrin, of cocain, of even such comparatively harmless substances as quinin, and, in fact, of nearly every known drug and of many articles of food, is almost daily observed by the busy medical practitioner. In all cases of poisoning the possibility of the existence of this unusual sensitiveness should not be forgotten.

Idiosyncrasy is presumably the cause also of certain rare cases in which poisons produce very unusual symptoms or even entirely opposite effects from those generally observed. Shearman³ reports a case in

¹ Jour. Pharm. and Exp. Ther., July, 1921, 17, No. 6, p. 433.

² On Poisons, 3d ed., 1875, p. 536.

³ Medical Times and Gazette, xiv (n. s.), p. 235.

which the taking of $1\frac{1}{2}$ grains of morphin was followed not by coma, but by convulsions resembling those caused by strychnin; and Philips¹ records an instance in which atropin caused contraction of the pupils instead of dilatation. Such cases are naturally likely to occasion mistakes in diagnosis and lead to much confusion in the event of a judicial inquiry; and their possibility, therefore, should always be borne in mind in forensic investigations.

3. Habit.—By the continued use of almost any poison, beginning with small doses and gradually increasing them, most persons may become habituated to their effects, and finally are able to take large quantities without the manifestation of toxic symptoms. This is shown in the case of habitual morphin-takers, many of whom, as is well known, are able to take doses that would prove rapidly fatal to those unaccustomed to its action. De Quincy, according to his *Confessions*, consumed each day a quantity of laudanum equivalent to about 360 grains of opium, and even this quantity of the narcotic has been greatly exceeded in more recently recorded cases. Russell² reports a case in which 60 grains of morphin were used daily hypodermically for some time, after which, for several months, 30 grains each of morphin and cocain were taken per diem. The arsenic-eaters of Styria, it has been claimed (but also strongly denied),³ take habitually such quantities of arsenic as would be fatal to the unhabituated, long use of the poison from early years having accustomed them to its effects. Van Fleet⁴ describes a case of alcoholic amaurosis in which strychnin was administered hypodermically in gradually increasing doses until the patient received $\frac{2}{3}$ grain twice a day, and this was kept up for a long time with marked benefit to the general health.

The tolerance of poisons gained by habit is, however, only relative; a sufficient increase of dose beyond the accustomed limit develops the usual toxic powers of the substance, and many cases are recorded of death among morphin habitués from quantities of the drug exceeding the amount to which they were habituated. At least one instance of this has come under my own observation. A woman of middle age, who for several years had been accustomed to take by the mouth from 2 to 4 grains of morphin two or three times a day, swallowed, either by mistake or with suicidal intent, not less than 10 or 15 grains of the drug. She soon fell into a profound stupor, exhibited all the usual symptoms of morphin poisoning, and died at the end of eighteen hours.

An interesting case of fatal cocain poisoning in a cocain habitué is recorded by Mancini.⁵

4. Tolerance.—Occasionally persons are found who manifest a remarkable natural tolerance of the action of certain poisons that is wholly independent of habituation. The author is acquainted with a physician who, although entirely unaccustomed to its use, is able to take

¹ Ophthalmic Record, January, 1903, xii, p. 5.

² Medical Record, 1902, lxii, p. 848.

³ Schwartze, E. W.: Jour. Pharm. and Exp. Ther., Oct., 1922, p. 181.

⁴ Manhattan Eye and Ear Hospital Reports, 1897, p. 15.

⁵ Revista critica di Clinica Medica, April 15, 1922, p. 121.

a grain of sulphate of morphin without the production of the slightest apparent effect. Christison¹ relates a similar but even more remarkable case of a man, unaccustomed to the use of opium, who took nearly an ounce of laudanum without any effect. Many other illustrations of similar tolerance are on record. No satisfactory explanation as yet has been afforded of this phenomenon.

In this connection it is interesting to note that several of the lower animals are quite immune to certain substances which are highly toxic to man. Rabbits, for example, eat belladonna leaves with a large degree of impunity; their flesh, however, becomes charged with the poisonous alkaloids of the plant, and is rendered toxic to man.²

5. **Disease.**—The action of poisons is not infrequently considerably modified by disease, their effects in some cases being materially increased, and in others greatly diminished. Organic diseases of the kidney, by retarding elimination, as a rule decidedly increase the effects of most poisons, a dose that would ordinarily not be overlarge sometimes producing serious results when the person is suffering from renal disorder. It should be stated, however, that the experiments of Meltzer and Salant³ and of Meltzer and Langmann⁴ seem to throw some doubt on this commonly accepted doctrine. Operating on nephrectomized rabbits and guinea-pigs they found that strychnin was fully as well borne by them as by normal animals.

On the other hand, delirium tremens, tetanus, and diseases attended with great pain, such as peritonitis and the passage of gall-stones, give the system a remarkable tolerance to anodynes like morphin, chloral, and chloroform. In these conditions doses of the anodyne may generally be administered which in a healthy adult would produce serious, or even fatal, results.

DIAGNOSIS OF POISONING

The diagnosis of poisoning before death is of the greatest importance in order that proper treatment may be directed, and also that accurate records may be made of the condition of the patient to be used in case of subsequent legal inquiry. Unfortunately, however, the diagnosis of poisoning is usually exceedingly difficult and frequently impossible in the living subject. This arises from the fact that, with the exception in most cases of corrosives (as a class) and of strychnin, the symptoms produced by poisons are not clearly characteristic, and cannot by themselves alone be distinguished with absolute certainty even by the most experienced observer from the symptoms of disease. Corrosive poisons, as a class, and strychnin, however, produce effects which when typically shown are so entirely characteristic as generally to leave no doubt as to their cause. (See also Brouardel's observations in the second paragraph on p. 38 of this volume.)

The **diseases simulating poisoning** are many, those resembling

¹ Treatise on Poisons, 1845, p. 33.

² Consult article by Firth and Bentley, *Lancet*, Oct. 29, 1921, p. 901, Belladonna Poisoning from Eating Rabbit.

³ *Jour. of Exp. Medicine*, 1902, iv, 107.

⁴ *Jour. of Med. Research*, Feb., 1903, ix, 19.

irritant poisoning being chiefly cholera, cholera morbus, acute indigestion, ulceration of the stomach or duodenum, gastritis, gastro-enteritis, peritonitis, appendicitis, hepatic and possibly renal colic, and intestinal obstruction; while those whose symptoms resemble *poisoning by neurotics* are, among others, hysteria, cerebral hemorrhage and thrombosis, epilepsy, the convulsions of certain organic brain diseases, tetanus, inflammation of the brain and its coverings, uremia, and organic heart disease.

As an aid to diagnosis we give below lists containing the commoner poisons and the diseases which produce the stated symptoms as their usual and expected effect¹; but it should be remembered that unusual and unexpected symptoms may follow the administration of almost any poison, and the same deviation may be shown by the symptoms of disease.

Vomiting (frequently associated with **purging** and abdominal pain).—

Poisons.—Arsenic, antimony, aconite, corrosive acids and alkalis, barium, colchicum, cantharides, digitalis, copper, iodine, mercury, phosphorus, phenols, wood alcohol, veratrum, zinc, poisonous foods.

Diseases.—Gastritis, gastro-enteritis, gastric and duodenal ulcer, cholera, cholera morbus, cholera infantum, uremia, acidosis, onset of many acute infectious diseases, the early stages of pregnancy, brain tumor.

Convulsions.—*Poisons*.—Aspidium, brucin, camphor, cyanids, san-tonin, strychnin.

Diseases.—Uremia, puerperal eclampsia, tetanus, epilepsy, many acute disturbances of the cerebrospinal system, especially meningitis.

Coma.—*Poisons*.—Opium and most of its derivatives, hydrated chloral, sulphonal, trional, veronal, paraldehyd, chloroform, cyanids, carbon monoxid, carbon dioxid, atropin, hyoscin, the various alcohols and phenols.

Diseases.—Uremia, puerperal eclampsia, acidosis, cerebral hemorrhage, cerebral thrombosis and embolism, brain injury, epilepsy and other brain diseases.

Dilatation of Pupil.—*Poisons*.—Belladonna, stramonium, hyoscyamus, scopolamine, and their derivatives, gelsemium, cocaine, nicotine.

Diseases.—Certain nervous diseases causing optic atrophy, sympathetic irritation, or weakness of oculomotor nerve.

Contraction of Pupil.—*Poisons*.—Opium and its derivatives, physostigma and its derivatives, pilocarpin, muscarin.

Diseases.—Certain nervous diseases, such as tabes.

General and Partial Paralysis.—*Poisons*.—Cyanids, carbon monoxid, carbon dioxid, botulism.

Diseases.—Apoplexy, brain tumor, meningitis.

Slow Respiration.—*Poisons*.—Opium and its derivatives, carbon monoxid.

Diseases.—Uremia, compression of brain as from hemorrhage.

Rapid Respiration.—*Poisons*.—Atropin group, cocaine, carbon dioxid.

Diseases.—Acute respiratory diseases, lesions of the medulla oblongata, hysteria.

¹ The author is indebted for valuable aid in constructing this table to Dr. Peter Bassoe and Dr. Ralph W. Webster.

Delirium.—*Poisons.*—Atropin group, cannabis indica, cocain.

Diseases.—Epilepsy, insanity, delirium tremens, organic brain diseases such as meningitis, visceral diseases such as nephritis.

Dyspnea.—*Poisons.*—Strychnin (during the convulsions), cyanids, carbon monoxid.

Diseases.—Diseases of cardiac and respiratory system, lesions of medulla oblongata and of vagus nerves.

Cyanosis.—*Poisons.*—Nitrobenzene, anilin, acetanilid, opium.

Diseases.—Same as under dyspnea, prolonged convulsions from any cause producing cardiac dilatation.

The careful consideration, in connection with the symptoms, of certain concomitant circumstances or conditions will often enable a physician to arrive at a conclusion of presumable accuracy, and sometimes to make an indisputably correct diagnosis. The presence on the lips and tongue and in the throat of marks of corrosion and the occurrence of shreds of mucous membrane in the vomited matter almost of necessity lead to the conclusion that a corrosive poison of some kind has been used, and the odor of the breath frequently discloses unerringly the administration of carbolic acid, chloroform, and the preparations of crude opium. The careful examination of vomited matter, and sometimes even of the feces, occasionally gives important evidence; the odor of carbolic acid, of cyanids, and of laudanum, the luminosity in the dark of phosphorus, and the slow solubility and crystalline character of particles of arsenic trioxid afford valuable aid in making a diagnosis. In the absence of these indications, and sometimes even in their presence, the following rules are frequently of great value in distinguishing acute poisoning from disease:

I. In cases of poisoning the symptoms usually appear suddenly and generally when the patient is in health.

II. In cases of poisoning the symptoms commonly make their appearance after the taking of food, drink, or medicine.

III. If several persons take the same food or drink, they all show similar symptoms.

Each of these points deserves separate consideration.

I. Diseases, as a rule, do not appear suddenly in persons in health, but usually are preceded by a number of hours, days, or even weeks of general or local indisposition; poisons, on the other hand, generally produce their symptoms suddenly, striking down persons in health with great severity and with but a short period of antecedent distress.

It should be remembered, however, that there are important exceptions to this rule on both sides. While nearly all poisons begin to show their effects, in the great majority of cases, within an hour or two at most after their administration, and, some, like the corrosives, hydrocyanic acid and strychnin, usually either almost immediately or within a few minutes, still many cases are recorded in which the full symptoms of the poison have been delayed a number of hours. Hartshorne¹ relates a remarkable instance of poisoning by a dram of arsenic trioxid

¹ Medical Examiner, 1855, p. 707.

in which the symptoms did not appear for sixteen hours; Christison¹ records a case in which upward of 2 ounces of tincture of opium was taken and no well-defined symptoms showed themselves till the eighteenth hour; and a case is reported² in which a woman ate a considerable quantity of aconite root, and no characteristic effects developed until ten hours afterward. The form in which the poison is administered and the condition of the stomach as to whether containing food or not are important factors, as we have already seen, in determining the rapidity of absorption and consequently the time of the production of symptoms.

On the other hand, diseases sometimes manifest themselves with great suddenness in persons enjoying apparently perfect health, as is seen occasionally in cases of apoplexy, heart disease, obstruction of the bowels, etc.

In cases of chronic poisoning, in which small but frequently repeated doses are ingested, the physician is very easily misled, as the symptoms under these circumstances resemble those of disease more nearly than when a single large dose is received. So, too, when in the progress of a disease a poison is taken, whether in one large or in several small doses, the diagnosis is rendered doubly difficult.

II. Sudden sickness setting in soon after taking food, drink, or medicine, especially if the symptoms are aggravated by taking additional quantities of the substance, is very suggestive of poisoning, and should always put a physician or attendant on his guard. Under these circumstances a careful examination of the suspected article will occasionally give important confirmatory proof by the taste, odor, altered general appearance, or presence of foreign particles. But it should be borne in mind that some diseases, such as acute indigestion, apoplexy, and perforation of the stomach, are prone to manifest themselves after eating or drinking, and that a number of other maladies are not infrequently increased in severity by taking food or drink.

III. If a number of persons who have taken the same food or drink manifest similar symptoms, the evidence of poisoning is usually quite strong. Suspicion of poisoning, however, should not of necessity be dismissed from the mind even if but one person shows symptoms of it and others who have partaken of the same food or drink escape, for it is quite possible that the poison may have been introduced into only a single portion of the food, or by chance that the other persons may have a tolerance more or less complete of the poison used. Numerous instances of these kinds, especially of the first, have been recorded. In the case of the State of Wisconsin *vs.* Zoldoske³ it was clearly shown that the deceased woman came to her death from strychnin taken in a piece of candy, although a number of other persons who ate candy from the same box experienced no ill effects.

While a careful observance of the above rules and a critical study of the symptoms presented frequently enable the physician to make a

¹ Treatise on Poisons, 1845, p. 544.

² Brown, The Lancet, October 6, 1860, ii, p. 344.

³ 82 Wisconsin, p. 530.

reasonably reliable working diagnosis, yet in order to distinguish poisoning from disease with absolute certainty during life a chemical analysis of the food, drink, or medicine taken, or, better still, of the vomited matter and urine, is generally necessary. Unfortunately, in the majority of cases of acute poisoning this is impracticable, the length of time necessary to make an accurate analysis for most poisons being too great. But for arsenic, mercury, and antimony we have in Reinsch's test a rapid, easy, and reliable means of detection, which every physician should be prepared to perform. For a description of this test see p. 50.

TREATMENT OF POISONING

The treatment of poisoning may be divided into four parts¹: I. The removal of the poison from the stomach; II. The administration of antidotes; III. The elimination of the poison; and IV. Counteracting the constitutional effects of the poison and sustaining the system.

In cases of industrial and other forms of chronic poisoning and also in cases in which the poison is introduced into the system by other avenues than the stomach, such as by inhalation, hypodermically, etc., the washing out of the stomach and the administration of chemical antidotes are not usually necessary.

I. The removal of the poison from the stomach may be accomplished either by inducing vomiting, or by the use of the stomach-tube. If, as is often the case, vomiting is already present, it is usually sufficient simply to encourage it by the administration of copious draughts of tepid water, with which preferably some greasy substance, like oil or lard, has been mixed. If, however, vomiting has not set in, or if it is not sufficiently copious, means should be used to produce it. Thrusting the fingers into the back of the mouth and depressing the tongue, or tickling the fauces with a feather, are commonly known procedures for inducing vomiting, but the surest means is the use of an emetic. Of these there are many, but perhaps the most useful are a dessertspoonful of ground mustard stirred up in a small cup of tepid water, 15 grains of zinc sulphate, 5 grains of copper sulphate, or, what is generally best of all, a $\frac{1}{10}$ grain of apomorphin hydrochlorid administered hypodermically. With children syrup of ipecac, in dose of from $\frac{1}{2}$ teaspoonful to 2 teaspoonfuls, according to the age of the patient, is the preferable emetic on account of ease of administration. Whatever method is employed, the vomiting should be kept up and the stomach thoroughly cleansed by the administration, as before described, of abundant draughts of tepid greasy water, in which appropriate antidotes may also be placed. Water in which dishes have been washed (dish-water) is often particularly useful to encourage vomiting—its greasy character, tepid temperature, and nauseating taste and odor make it especially efficient whenever its slight alkalinity, due to the presence of soap, and its fat content are not objectionable.

The stomach-tube is usually to be preferred to emetics both because

¹ See Cheinisse, *Presse Méd.*, 1920, xxviii, 858.

it produces less prostration and is generally somewhat more efficient in completely removing the poison. It should be introduced with care in order to avoid injury to the parts with which it comes in contact. As a rule a pint of tepid water should at once be introduced into the stomach through the tube and removed by suction with a pump (see Fig. 1), or by means of a large strong rubber bulb, and the operation repeated a number of times or until it is evident that the contents of the stomach

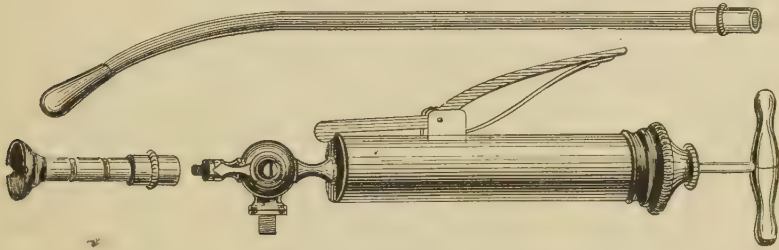


FIG. 1.—Stomach-pump.

have been completely washed out. Antidotes may generally advantageously be placed in the water, as a portion almost always remains in the stomach and delays the action of the poison.

Instead of a tube to which a pump or suction bulb is attached, a long soft rubber tube with funnel and exhaust bulb (see Fig. 2) may be used and the contents of the stomach, after dilution with water, removed by syphonage with the aid of the exhaust bulb. In the absence of a stomach-tube a piece of ordinary rubber gas-tubing with a

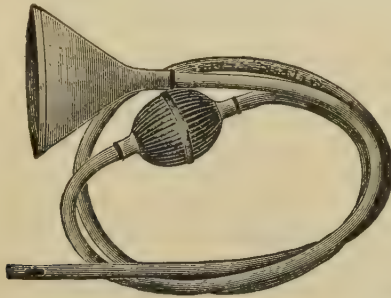


FIG. 2.—Soft-rubber stomach-tube, with funnel and exhaust bulb.

funnel inserted in one end may be used to draw off the contents of the stomach by syphonage.

If the contents of the stomach consists to a considerable degree of large pieces of food it is impossible to empty the organ completely by a tube owing to the narrow caliber of the latter, and it is necessary to secure evacuation of the stomach in the beginning, at least, by an emetic, after which the tube may be used for washing out the stomach more thoroughly.

However the stomach is emptied, the contents should be received in perfectly clean bowls or buckets and carefully inspected to ascertain if any poison recognizable by its physical properties is present. The odor of carbolic acid; luminous particles of phosphorus; heavy, white, slowly soluble grains of arsenic trioxid (arsenious acid), etc., are frequently important guides in determining the exact character of the poison used and in directing appropriate treatment. It is desirable in all cases to save a part or all of the material ejected for subsequent chemical analysis, in case of legal inquiry.

In poisoning by the corrosive acids and alkalis it is generally considered inadmissible by most authorities to use either emetics or the stomach-tube, on account of the danger of producing perforation of the stomach or esophagus from the softening of these parts by the corrosive agent. In this form of poisoning it is commonly recommended that reliance be placed on copious dilution by water or milk and the use of appropriate chemical antidotes.

Hemmeter,¹ however, differs with most of the writers in regard to this matter, and I believe with reason. He says: "In 6 cases of poisoning—one with lye, two with oil of vitriol, one with strong ammonia, and two with carbolic acid—the tube was used immediately after the patients reached the hospital. As such cases run great danger of a corrosive perforation we have personally used the tube and let the patient take his chances, which were better in these cases than in those where the tube was not used." He says further: "We make so explicit a statement of treatment because we had experience with 2 cases where the autopsy showed that recovery might have been possible (as not much sulphuric acid had reached the stomach) if the treatment had been more heroic—*i. e.*, if the tube had been used for the timely removal of the poison."

In whatever way the stomach is evacuated it should be done thoroughly, and the washing out of the organ should be continued until the wash water returns nearly clear and almost free from odor.

II. Antidotes are of two kinds: 1. Those that act mechanically; 2. Those that act chemically.

1. Antidotes that act *mechanically* are either those that envelop the poison in some insoluble material, or those that coat the mucous membrane of the stomach in a similar manner; in either case the result being a very greatly reduced rate of absorption of the poisonous body. The most important of these substances are fats and oils, milk (on account of the coagulum of casein formed in the stomach), the white of eggs, and charcoal in a moderately fine state of subdivision. The latter acts by absorbing the poison within its pores, and is especially efficient in connection with the organic poisons. Fantus² by numerous experiments has shown the value of fuller's earth and of other similar substances in the treatment of certain forms of poisoning; and Schwartze³ has demon-

¹ Diseases of the Stomach, 2d ed., 1900, p. 443.

² Fantus, Jour. Amer. Med. Assoc., 1915, 64, p. 1838.

³ Jour. Pharmacology and Exp. Ther., February, 1922, p. 52.

strated by tests on animals the retarding effect of diatomaceous earth on poisoning by strychnin. Fats and oils are of very wide utility, both on account of materially retarding the absorption of the poison and also by protecting the mucous membrane of the stomach from corrosive or irritant action; in case of poisoning, however, by a few substances, such as phosphorus, camphor, aspidium, and cantharides, they are entirely inadmissible, as they dissolve the poison and render it much more active, and, for the same reason, milk is undesirable unless it has been well skimmed. Atkinson¹ advises the use of liquid petrolatum as a solvent for unabsorbed phosphorus in cases of phosphorus poisoning, as this paraffin oil is not absorbed and thus possesses advantages which the vegetable fats and oils do not have. It is sometimes stated that milk is also inadmissible in poisoning by arsenic trioxid, its alkalinity favoring solution of the poison, but this objection is not well grounded, since the reaction of cows' milk is practically always feebly acid, at least to phenolphthalein.²

2. The proper *chemical antidote* for each poison will be given later on in the discussion of the individual poisons, and only a few points of general interest need be considered here.

The majority of antidotes that act chemically do so by reacting with the poison to produce an insoluble or sparingly soluble compound, and one therefore that is either inert or of only slight toxicity. The use of common salt as an antidote in poisoning by silver nitrate is an illustration of this, insoluble and consequently harmless silver chlorid being produced by the chemical action of the antidote upon the poison. Some, however, act by changing the chemical character of the poison without the production necessarily of an insoluble body, as is the case when acids are used to neutralize caustic alkalis, and when potassium permanganate is administered as an antidote to morphin. It should always be borne in mind in the use of chemical antidotes, in whatever way they act, that the compounds produced are often only relatively harmless, and that if allowed to remain in the stomach for some time serious results may be produced; thus, ferric hydroxid when used to antidote arsenic unites with the latter, producing a compound of very sparing solubility in pure water, but as it is soluble in dilute acids, it is liable to be dissolved and the poisonous properties of the arsenic redeveloped if allowed to remain in the stomach for some time. In all cases, therefore, it is well after the administration of an antidote to empty the stomach, repeating the operation a number of times.

In the selection of a chemical antidote a substance should always be chosen, when practicable, which is by itself as nearly harmless as possible, so that if an excess is given it will do little or no damage. Thus, in choosing an acid to antidote a corrosive alkali, vinegar or lemon-juice is greatly preferable to sulphuric or hydrochloric acid, which if given in too large quantity might occasion as much injury as the original poison.

¹ Jour. Lab. and Clin. Med., 1921, 7, 148. See also under Phosphorus, p. 150.

² Duclaux, Principes de laiterie, p. 27.

If a case of poisoning is seen late, and especially if free vomiting has already been established, it is often assumed that no poison remains in the stomach, and that consequently antidotes are unnecessary. Such, in fact, is often the case, but it is by no means always so. Antidotes, whether acting chemically or mechanically, should not only be given as early as possible, but their administration should be kept up until it is absolutely certain that no more of the poison remains in the stomach. Some poisons, especially arsenic in the form of the trioxid, are prone to persist in the stomach for many hours, frequently in spite of profuse vomiting. In a case examined by the writer, in which death occurred eighteen hours after the administration of a teaspoonful of arsenic trioxid, and in which copious vomiting had continued for several hours, a fraction more than 6 grains of the poison was found in the stomach after death, largely in the undissolved form, adhering closely to the mucous membrane. In another case in which death took place forty-eight hours after an unknown quantity of arsenic trioxid had been taken for suicidal purpose, nearly 2 grains of the undissolved poison were found in the stomach. Profuse vomiting had occurred soon after the poison was taken, and the physician who was called in twelve hours later thought it unnecessary to wash out the stomach or give antidotes, unfortunately feeling convinced that all the poison had been necessarily removed by the abundant vomiting.

It must be admitted that it is sometimes extremely difficult to determine when all the poison has been removed from the stomach, and when antidotes, therefore, may be safely discontinued; the use of Reinsch's test, however, in case of poisoning by arsenic, antimony, or mercury, gives us conclusive information, and the odor of the vomited material is of great service in arriving at correct conclusions when carbolic acid or other poisons of characteristic odor have been taken. In poisoning by opium and its derivatives it is especially important to continue the use of antidotes, as it is well known that however these poisons are administered, their poisonous morphin, is eliminated to a considerable degree by the mucous membrane of the stomach; washing out that organ, therefore, and the administration of antidotes are serviceable at almost all stages.

Tincture of iodine well diluted with water, tannic acid, and dilute solution of potassium permanganate are valuable antidotes in a large number of cases of poisoning. The first two precipitate practically all poisonous alkaloids and many glucosids, and the permanganate by its active oxidizing power tends to detoxicate several important poisons, such as morphin, phosphorus, and poisonous mushrooms.

Universal Antidote.—In case no information is at hand in regard to the nature of the poison taken, it is evident that the exact antidote cannot be administered. Under these conditions, however, it is not infrequently highly advantageous to give a combination of two or more substances of a harmless character which are efficient at least in a moderate degree in antidoting a number of poisons. Several combinations of this character have been suggested. Perhaps none serves the

purpose as well as a mixture of pulverized charcoal, tannic acid, and magnesia (magnesium oxid), using about two parts of the first to one part each of the other two. The mixture may be given in doses of a heaping teaspoonful stirred up with water and may be frequently repeated, as none of the constituents is harmful. The charcoal acts physically, taking up alkaloids and many other poisons into its pores, greatly retarding their absorption by the system; the tannic acid (as stated above) precipitates alkaloids, certain glucosids, and many of the metals; and the magnesia neutralizes acids, and, next to ferric hydroxid, is probably our best antidote for arsenic. The mixture, consequently, antidotes more or less efficiently a wide range of poisons and, somewhat questionably however, has received the appellation "universal antidote." It should not be used to the exclusion of more thoroughly appropriate antidotes when the exact nature of the poison is known; and with this, as with all other antidotes, vomiting should be encouraged or the stomach washed out shortly after the administration of each dose, except a final one, which is preferably left in the stomach.

Physiologic Antidotes.—The antidotes we have been considering act either mechanically or chemically; but there is another class of bodies often used in the treatment of poisoning which produce their effect purely by physiologic action, and hence have been designated "physiologic antidotes." Such are atropin in the treatment of poisoning by morphin, and chloroform in strychnin-poisoning. The term "physiologic antidote," however, has been objected to, and perhaps justly, for such substances do not truly neutralize the poisons for which they are given, but simply antagonize their effect, and that, too, only in part. On this account the more appropriate term for them is undoubtedly *physiologic antagonists*. Probably the best example of physiologic antagonism is that shown by atropin and physostigmin. Atropin accelerates the heart's action, while physostigmin slows it; atropin dilates the pupil, while physostigmin contracts it; atropin arrests glandular secretion, while physostigmin increases it; atropin stimulates, while physostigmin depresses the central nervous system. In most other cases, however, the antagonism is usually limited to only one or two of the effects produced, their action in other ways not infrequently being synergistic. Thus atropin increases the reflex function of the central nervous system, while morphin lessens it, and consequently the former in small doses may be used with advantage as a partial physiologic antagonist in the treatment of opium-poisoning; but in other respects there is little or no real antagonism—in fact, their toxic action in certain ways coincides, and, consequently, if atropin is administered in opium-poisoning it should be only in limited quantity.

Among other physiologic antagonisms may be mentioned atropin to pilocarpin, strychnin to nicotin, digitalis to aconite, chloral to strychnin, caffeine to morphin, and each of them has been used in the treatment of poisoning by the other.

III. In the majority of cases of poisoning it is the poison that enters the circulation that produces most or all of the harmful results, and it

is exceedingly important therefore that **elimination** should be encouraged, so that the dangerous agent may be removed from the body as soon as possible. The experiments of Claude Bernard, showing that if the elimination and the absorption of a poison are kept equal harmful results do not appear or are reduced to a minimum, are of great interest in this connection. Unfortunately our means for quickly producing elimination are generally not immediately available, and consequently in acute poisoning by rapidly acting poisons, treatment by elimination is usually but little practised; in subacute and chronic cases, however, it is of the greatest value and should always be used.

The chief emunctories by which poisons are eliminated are the kidneys, skin, and bowels, and all of these therefore should be stimulated to their fullest activity. The kidneys are of special importance, as in the majority of cases they are the chief avenue of elimination of most poisons. Diuretics, consequently, should be exhibited, and of these perhaps the best is pure water copiously administered after the poison has been removed from the stomach; and small doses of potassium acetate, digitalis, caffeine, theobromin, or other similar diuretics may be added, if not otherwise contraindicated. Walker and Dawson, however, have shown by experiments on animals that diuretics are useless or even harmful if there is acute nephritis.¹ Hot applications over the region of the kidneys will sometimes promote their activity, especially when they are congested by the irritant influence of the poison. The urine should not be allowed to accumulate in the bladder, but should be drawn off by a catheter from time to time, if the patient is unable to void it naturally. The bowels, if inactive, should be emptied by enemas of tepid water or by the administration of mild laxatives, and the skin should be kept active preferably by warmth, but medicinal diaphoretics, such as pilocarpin given hypodermically, are sometimes of great utility, especially if the kidneys persistently refuse to perform their office.

The success obtained in certain diseases of toxic origin, such as puerperal eclampsia and uremia, by the hypodermic injection of normal salt solution (hypodermoclysis), has led to the application of the same measure to the treatment of poisoning. The remedy acts by diluting the poison in the blood and by favoring the action of the eliminative organs, especially of the kidneys. The operation is performed by attaching an ordinary irrigator to a large hypodermic needle, taking care that the liquid used and everything about the apparatus are thoroughly sterile. The solution can be made with sufficient accuracy by dissolving a heaping teaspoonful of common salt in a quart of boiling water. Sodium bicarbonate and certain other salts have at times been used to replace, in part, the sodium chlorid. It should be administered at a temperature of about 110° F., and a quart is generally used, although half or a quarter of this quantity is sometimes to be preferred. In cases where some delay in its action is permissible the warm salt solution may advantageously be administered by the lower bowel (enteroclysis),

¹ Arch. Int. Med., 1913, 12, p. 171.

as there is then no danger of infection from imperfect sterilization. On the other hand, in case of poisons that act with great rapidity we may resort to the intravenous injection of the saline solution. For this purpose Fischer's solution¹ (composed of crystallized sodium carbonate [Na_2CO_3 , $10\text{H}_2\text{O}$] 10 gm., sodium chlorid 14 gm., and distilled water to make 1000 c.c., and thoroughly sterilized) is especially useful. Or one may use a solution of pure glucose, as practised by Woodyatt, Sansum, and Wilder.²

Numerous cases showing the value of the above treatment by saline infusion are on record. Typical among them I may refer to a case reported by Hirsch and Edel³ of phenyl-hydroxylamin poisoning with recovery, after the use of stimulation and venesection followed by the subcutaneous injection of a liter of a solution containing 0.3 per cent. of sodium chlorid and 0.4 per cent. of sodium bicarbonate; and to a case of poisoning by 8 grains of morphin taken hypodermically reported by Willoughby,⁴ in which after strychnin, atropin, and other measures had been unsuccessfully tried, the infusion of a liter of salt solution in the flank led to a rapid recovery. But Sansum,⁵ experimenting with animals poisoned by mercuric chlorid or by diphtheria toxin, did not find any favorable results following intravenous injections.

The efficiency, however, in general of saline infusion in promoting elimination, and thereby removing poisonous substances from the body, cannot be doubted and is strikingly shown by the experiments of Luckhardt and Rosenbloom⁶ with parathyroidectomized dogs.

IV. In most cases it is the **systemic effects of poisons** that are chiefly dangerous, and these, therefore, as well as the local action, should be combated from the beginning. Anodynes should be administered for the control of excessive pain; strychnin, nitroglycerin, and digitalis given for threatened heart failure; and artificial respiration or faradization of the phrenic nerve used in the event of failure of respiration. Inhalations of pure oxygen are often of service in case of deficient oxygenation of the blood, and chloral or chloroform is of great value in controlling convulsions resulting from heightened reflex irritability. The patient, as a rule, should have his strength conserved by being kept quietly in bed, and the fewest possible outsiders should be allowed in the room. Artificial heat must be employed in case of coldness of the surface or of the extremities, and general stimulants, such as alcohol in small doses, ether subcutaneously, ammonia by inhalation, or by the mouth in the form of the aromatic spirit, and strychnin, preferably by hypodermic injection, should be used as indications arise.

In poisoning by the heavy metals, especially by mercury, laboratory

¹ Martin H. Fischer: *Edema and Nephritis*, 3d ed., 1921, p. 680.

² *Jour. Amer. Med. Assoc.*, 1915, 65, p. 2067.

³ *Berlin. klin. Wochenschr.*, 1895, xxxi, p. 891.

⁴ *The Lancet*, 1902, i, p. 1316.

⁵ *Jour. Amer. Med. Assoc.*, March 23, 1918, 70, p. 824. *Ibid.*, March 30, 1918, 70, p. 904.

⁶ *Proc. Soc. Exp. Biol. and Med.*, 1921, vol. 19, p. 129; *Science*, July 14, 1922, p. 48.

experiments¹ and clinical experience² demonstrate the value of the liberal use of alkalis, either by the mouth, by the rectum, or by intravenous injection, both for their systemic action and to promote elimination.

In connection with each poison later on special details of treatment will be given.

POSTMORTEM EXAMINATION

The postmortem examination should be conducted as directed in the article on that subject on page 78 *et seq.* of this volume. A few special points only need be considered here.

In case of suspected poisoning it is often thought sufficient to examine the alimentary tract alone; this view, however, is entirely incorrect, and in all cases a thorough examination of all parts of the body should be made, both to determine the presence or absence of disease and to disclose the remote effects of the poison. It is only by making a complete investigation that entirely reliable results can be secured, and this is especially important in the event of a judicial inquiry, when the exclusion of death from disease of the kidneys, heart, brain, or other distant parts is often of great value. It is also frequently considered sufficient in cases of suspected poisoning to remove the stomach only for chemical analysis, but this likewise is a mistake; a part of the bowels, both kidneys, and the liver should in all cases also be removed for chemical investigation, and it is desirable in most instances to preserve the brain, spinal cord, heart, any urine that may be found in the bladder, and a quantity of the blood; if death from chloroform, ether, or other anesthetic is suspected the lungs also should be removed for examination.³

Each organ should be placed in a separate wide-mouthed glass jar, and it is seemingly almost unnecessary to add that these and everything else with which the organs come in contact should be scrupulously clean. Occasional mistakes, however, have arisen from neglect of this point. The writer is personally acquainted with a case in which the life of an unquestionably innocent man was placed in jeopardy by the discovery of arsenic in lethal amount in the remains of his wife, who died somewhat suddenly, although without the slightest symptoms of arsenical poisoning. It was subsequently demonstrated that the poison entered the organs at the time of the postmortem examination by their being placed in a bowl carelessly supposed to have been clean, but which really had adhering to it a small amount of a highly arsenical embalming fluid.

The jars containing the different organs should be carefully sealed as soon as practicable after the parts have been placed in them. An excellent means of accomplishing this is to wrap each jar separately in a piece of firm paper, which should be held securely in place by narrow tape or stout twine passing over and around the jar several times. Melted sealing-wax should be dropped over the top and bottom of the

¹ Martin H. Fischer, *Edema and Nephritis*, 3d ed., 1921, and Martin H. Fischer, *Soaps and Proteins*, 1921.

² H. B. Weiss, *Jour. Amer. Med. Assoc.*, 1918, 71, p. 1045; J. Rosenbloom, *Amer. Jour. Med. Sci.*, 1919, 152, p. 348.

³ See Vaughan, *Jour. Lab. and Clin. Med.*, 1919, 2, 286.

package as well as at numerous points on the exposed edge of the wrapping-paper and at intervals on the tape or twine, and impressions made in the wax with a private seal, or, in case this is not at hand, with the seal of a bank or express company or with some rare coin. The wax should not be put on the jar itself, as it is exceedingly difficult and sometimes impossible for the toxicologist subsequently to open the jar without particles of the wax dropping in and contaminating the contents. If the sealing is properly done, it is quite impossible to gain access to the jar without mutilating the package, and it affords a perfect safeguard, therefore, against secret tampering with the organs while they are being conveyed to the chemist or the pathologist for examination.

It is better to add nothing to the organs to preserve them; it is preferable to prevent decomposition by keeping them in a cold place. If refrigeration, however, is not available a little pure alcohol may be used as the least harmful of any preservative, a few ounces of the alcohol used being reserved and sent to the chemist with the organs to be tested, if necessary, for the presence of extraneous substances. Formaldehyd in small amount may be used instead of alcohol in case of necessity, but as it is liable to interfere seriously with the detection of certain poisons, especially the cyanids, its use is not to be recommended. The author is personally acquainted with 2 cases of unquestionable poisoning by sodium cyanid in which formaldehyd was used as a preservative agent and the detection of the poison entirely prevented by the complete destruction of the cyanid by the formaldehyd.¹

The evidences afforded by a postmortem examination in a case of suspected poisoning are important, but are rarely conclusive. With the exception of the corrosives, whose caustic effects on the mouth, throat, and stomach are often entirely characteristic, no poison produces appearances that are not practically identical with those that *may* be occasioned by disease or other natural causes. It was formerly believed, and among the uninformed it is still supposed, that rapid decomposition of the body and extensive discoloration are evidence of death from poisoning; this, however, has long since been thoroughly disproved, poisons having no specific action in accelerating putrefaction, but, on the contrary, some of them, like arsenic and mercury, at times appear to have a preserving influence. Extreme rigidity of the muscles after death is generally produced by strychnin, but equal rigidity may be occasioned by ordinary rigor mortis, and in exceptional cases it may persist as long from the latter cause as from strychnin; a dark fluid condition of the blood usually follows poisoning by belladonna, aconite, and many other neurotic poisons, but a similar state is produced by uremia and by certain infectious diseases; fulness of the vessels of the brain is usually seen as the results of opium-poisoning, but the same condition is occasioned by inflammation of the brain and many other cerebral diseases; the congestion of the spinal cord which generally follows death from strychnin is also observed after death from tetanus, hydrophobia, and spinal meningitis; fatty degeneration of the liver and other

¹ Compare p. 685.

internal organs is often produced by phosphorus and arsenic, but it is also found as the result of age and of certain diseases, such as tuberculosis, puerperal eclampsia, and acute yellow atrophy; and redness of the stomach and bowels, which are the commonest of all the postmortem indications of irritant poisoning, are uniformly observed as the consequence of the gastritis and gastro-enteritis of disease.

Brouardel¹ records numerous instances of sudden death from ulceration and perforation of the stomach and bowels, from rupture of the heart, gall-bladder, and Fallopian tubes, from intestinal strangulation and impacted gall-stones and feces, from unsuspected diabetes and Bright's disease, and from other causes of auto-intoxication which in a marked degree presented the symptoms of acute poisoning. Failure to excrete the toxic substances produced after an exceptionally hearty meal or excessive indulgence in alcohol may likewise, he states, cause death under conditions which might suggest poisoning. According to this authority, in from 25 to 30 per cent. of all cases of sudden death, no lesion can be discovered to which it can be referred.

Death may occur from poisoning and no postmortem evidences of it be discoverable, and many cases of this kind are on record. Even the appearances that are the most characteristic, and which are usually looked for with the greatest confidence, may be entirely wanting. Casper² records a case of death from strychnin in which there was not only no unusual rigidity of the muscles, but no other evidence of death from the poison; and in the case of Lucy Heideimeyer, which the writer investigated in 1887, the stomach and bowels showed not the slightest evidence of irritation, but, on the contrary, the mucous membrane was paler than usual, although she died of acute arsenical poisoning, as a legal inquiry clearly demonstrated.

The chief value of a postmortem examination in a case of suspected poisoning, aside from securing organs for chemical analysis and other scientific investigation, lies (1) in determining whether such appearances are present as are usually produced by poison, or at least are compatible with it, and (2) in disclosing the presence or absence of natural causes of death. In regard to the first of these points, it should be borne in mind, however, that the postmortem appearances produced by no poison are always the same, and sometimes, as before stated, even the most characteristic marks may be wholly absent; and concerning the second point it is scarcely necessary to state that death may occur from poison even though the person at the time was suffering from a serious or even necessarily fatal malady.

No postmortem investigation can be considered entirely complete without a careful microscopic examination by a competent pathologist of at least the heart, kidneys, and liver, and also, if possible, of the brain and spinal cord. When practicable, a bacteriologic examination of certain portions of the body, especially the liver, spleen, kidneys, lungs, and the heart's blood, should be made to determine the presence

¹ *Annales d'hygiène publique*, 1902, xlvii, p. 12.

² *Vierteljahrsschr. f. gericht. Med.*, July, 1864, i (n. f.), p. 7.

or absence of bacteria, which we know may sometimes be the cause of fatal symptoms similar to those produced by some poisons. A bacteriologic and microscopic examination of the bowels may also be useful in cases of suspected poisoning showing dysenteric symptoms. These extended tests and examinations, however, while always desirable from a scientific standpoint, and, in case no poison is found in the body by chemical analysis, highly important, are rarely if ever essential to the investigation of a case when poison is discovered in well-marked quantity.

CHEMICAL ANALYSIS

Since it is only in exceptional instances that a case can be positively established as one of poisoning, either by the symptoms or the post-mortem appearances, or even by both combined, a final decision in regard to the matter can generally be reached solely by the aid of a chemical analysis. It should not be understood, however, that in all instances a chemical analysis is indispensable to prove that death resulted from poison, or that, in event of an analysis, the finding of poison is essential, for outside circumstances may be of such a conclusive character, and, in occasional instances, the symptoms and postmortem appearances may be so characteristic, as to remove all doubt as to the nature of the case. In the well-known Palmer-Cook case¹ that occurred in England in 1855, Palmer was tried, convicted, and executed for killing Cook with strychnin, although chemical analysis failed to reveal the presence of the poison in the body after death; the incriminating circumstances were so strong, and the symptoms displayed by the deceased so characteristic, as to prove conclusively the guilt of the accused.²

It is commonly supposed that the stomach with its contents is the only organ necessary for chemical analysis in a case of suspected poisoning. While it is true that in most cases the stomach is the most desirable part of the body for examination, other organs should, whenever possible, also be submitted to analysis, and of these the most important, as a rule, are the liver, kidneys, and bowels, in the order in which they are named. The brain, spinal cord, heart, blood, and urine are frequently of service, and, in fact, there is scarcely a part of the body that may not be examined with profit. In the case of a man who died of suspected poisoning at Fort Collins, Colorado, in 1890, the discovery of arsenic in the muscles, skin, and bones furnished important evidence after all the viscera and the brain had been removed and consumed in inconclusive tests. It should be remembered that the poison found in the stomach and that extracted from the other organs have a quite different relation. The poison in the stomach is not, as a rule, the toxic

¹ For a full account of this celebrated case, see Tardieu, *Ann. d'hygiène*, 1856, vi, p. 371 *et seq.*

² It should perhaps be stated that Palmer's guilt has not been universally admitted. Brouardel (*Ann. d'hygiène*, 1902, xlvii, p. 28), after reviewing the case, concludes that Cook died not of strychnin-, but of uremic poisoning. The post-mortem examination showed, he believes, that the deceased was suffering from undiscovered Bright's disease, and that excessive indulgence in alcohol and the table brought on a sudden attack which ended his life. Brouardel, however, evidently overlooks the moral circumstances, some of which were almost overwhelmingly convincing.

material that has produced death; it has not yet entered the circulation, and any damage that it may have done is purely local; on the other hand, the poison in the liver, kidneys, brain, etc., is the part that has caused the death of the person; it has been absorbed, has circulated in the blood, and has been deposited in the parts from which it is extracted. It should also be borne in mind that a person may die from the effects of a poison, and none be found in the stomach, it having been entirely removed from that organ by vomiting and absorption. It is true that after death from poison none of the latter may be found by analysis in any part of the body, but it is more likely to have disappeared entirely from the stomach than from the other organs.

In addition to the various parts of the body, vomited matter, suspected food, any urine that may have been passed during life, medicines, and clothing may often be submitted to chemical examination with great profit, important light frequently being thrown on a case by the results of such an investigation. In the Maybrick case the discovery of arsenic in the handkerchief and in the clothing of the accused constituted one of the most important evidences against her.

The chemist who is called upon to make the analysis should be not only one who is thoroughly trained in general chemistry but also one who has a good knowledge of anatomy, physiology, materia medica, and toxicology. His integrity should be above the remotest suspicion. The suggestion¹ that two chemists should perform the analysis together, and should conjointly give testimony regarding the results, is an excellent one, and should be carried out whenever practicable. The sole objection to this plan is the greatly increased expense, but when life, liberty, and reputation are at stake this ought not to weigh.

The analysis should be conducted in a room whose doors and windows are kept locked and sealed at all times when the chemist is not personally present; no one except the analyst himself should be admitted to the room during the progress of the investigation, and under no circumstances should any poison, other than the reagents used in the analysis, be permitted in the apartment. All chemicals used in every operation should be known from actual tests by the chemist himself to be free from all impurity; the guaranty of dealers in chemicals should never by itself alone be depended upon. It is exceedingly desirable that coincident with the analysis of each part a blank test should be made in which an artificial mixture of foods, or a part of a calf's liver, equal in weight to that of the organ operated upon, is subjected to exactly the same procedure as is the part in question, the same chemicals in the same quantity being used in both. Unless the result of the blank test shows no poison the analysis of the suspected organ cannot be depended upon.

It is sometimes urged² that in every analysis for poison new apparatus should be used. In the opinion of the writer, however, this is not

¹ R. Ogden Doremus, *The Forum*, Oct., 1893.

² Dragendorff, *Ermittelung der Giften*, 1895, p. 14; Reese, *Manual of Toxicol.*, p. 243.

only not necessary, but is scarcely to be recommended. It is well known that articles of glassware, and sometimes of porcelain, occasionally contain arsenic and other poisonous metals which may be imparted to material placed in contact with them. For this reason it is far better to use apparatus which has previously been employed in a blank test that has given negative results, conclusive evidence being thus obtained that none of the vessels contain poisonous constituents, or at least yield none to the material under examination. It seems almost unnecessary to add that every piece of apparatus must be scrupulously clean. Each article should be washed separately just before using it, preferably first with dilute alcoholic solution of potassium hydroxid, then with warm dilute hydrochloric acid, and finally with an abundance of warm water.

As a rule some indication is afforded by the symptoms, postmortem appearances, or circumstances surrounding the case of the poison that may be present, and this is often a most important guide in conducting the chemical analysis. This is especially true in those numerous cases in which, on account of expense or lack of sufficient material, a direct test must be made for one poison or group of poisons. In all instances, however, where it is practicable a complete search should be made, so as not only to determine fully what poison or poisons are present but also to afford, what in many cases is of nearly equal value, evidence of the absence of other toxic substances.

Previous to beginning the chemical examination of any organ it should be thoroughly inspected and weighed; and in case of the contents of the stomach, vomited matter, blood, or other fluid or semifluid substances, the material should also be measured. The interior of the stomach and the stomach contents should be most critically examined, both with the unaided eye and with a hand magnifying-glass, for the presence of undissolved poisons, such as arsenic trioxid, Paris green, lumps of opium, and the seeds, leaves, and other parts of poisonous plants, and also for mechanical irritants, like powdered glass. The evidence thus afforded is frequently of the most convincing character. The odor of the material should also be carefully determined and the reaction to litmus-paper observed. In case of the contents of the stomach or of vomited matter the closest attention should be paid to the nature of the food present, a microscope of medium power often being used with great advantage to demonstrate the presence or absence of starch granules, muscular fiber, and vegetable tissue, and to disclose their exact character. The identity of the material under examination and very many other points are not infrequently established by the evidence thus obtained.

The first step in a chemical analysis for poisons is usually the separation of the latter from the accompanying organic material, and the processes in general for accomplishing this are given below. It is only after such separation, and subsequent purification if necessary, that chemical and physiologic tests can ordinarily be applied with any degree of certainty, the presence of complex organic matter generally being fatal to the development of conclusive reactions for most poisons. In

connection with each individual poison the characteristic tests for it will be given, and also the methods which may be employed for extracting it from the various organs; we give below, however, a systematic procedure for separating poisons in general, and while in many cases this scheme may advantageously be simplified or modified in many ways, the general principles involved are such as are most usefully employed in nearly all instances.

The substance to be analyzed should first be very finely comminuted with a pair of sharp scissors, chopping-knife, or hashing machine, or by pulverizing in a mortar, and it is then divided into three equal portions, one to be set aside for use in case of accident or for additional tests if any are needed; another to be used for the extraction of volatile and subsequently of mineral poisons; and the third to be employed for the detection of non-volatile organic poisons.

In some cases when the amount of material is very small, or the quantity of poison present is believed to be minute, it may be necessary to divide into two parts only, one for the volatile and mineral poisons, and the other for the organic poisons, no portion being set aside as a reserve. So, too, if circumstances point to the administration of a corrosive acid or alkali, it is necessary, if a complete examination is to be made, either to divide the material into four parts (one being used for testing for these substances and the others disposed of as above), or to devote the third reserved portion to this purpose. It is obviously, however, very important whenever practicable to keep some part of each organ or substance tested as a reserve supply. Accidents may happen even with the most careful manipulation, or additional and unexpected tests may be needed as the investigation proceeds, and the reserved part may become almost indispensable.

If the process is properly conducted, the same portion of material may be used without loss or other inaccuracy for the separation of volatile poisons and then for the detection of mineral substances.

Separation of Volatile Poisons.—The material brought to the consistency of a thin gruel by the addition of distilled water if necessary, and made of slightly acid reaction (if not already so) by adding a little tartaric acid, is placed in an apparatus for distilling in steam, which is connected with a Liebig condenser through which very cold water circulates (Fig. 3). Heat is carefully applied and the distillate is collected in several fractions, each one amounting in volume to about one-fifth of the material in the flask. If a specific volatile substance is suspected, a definite temperature of distillation may be advisable. The operation should be conducted in a dark room, and with a screen placed between the flame of the lamp and the condenser, in order that any phosphorescence, indicative of the presence of phosphorus in the material under examination, may be seen.

After three or four fractions have been collected, or sooner if it appears that nothing further is distilling over, the apparatus is allowed to cool and magnesia carefully added until the mixture is of very feebly alkaline reaction. The mixture is then again distilled as before.

The *distillate from the acid mixture* may contain (among other less important volatile poisons) alcohols, aldehyds, ethers, carbolic acid and other phenols, bromin, iodin, phosphorus, camphor, chloral, chloroform, turpentine and other volatile hydrocarbons, essential oils, nitroglycerin, nitrobenzene, benzoic acid, salicylic acid, hydrocyanic acid, hydrochloric acid, and other volatile acids.

The *distillate from the alkaline mixture* may contain ammonia, anilin, coniin, nicotin, and other volatile bases.

To each of these distillates the appropriate tests for the several poisons that may be present are to be applied as directed in subsequent chapters in connection with the individual poisons.

A number of the substances in the above lists, such as camphor, salicylic acid, anilin, coniin, nicotin, and other volatile bases, may appear also in the results of the examination for organic poisons, as will be seen later.

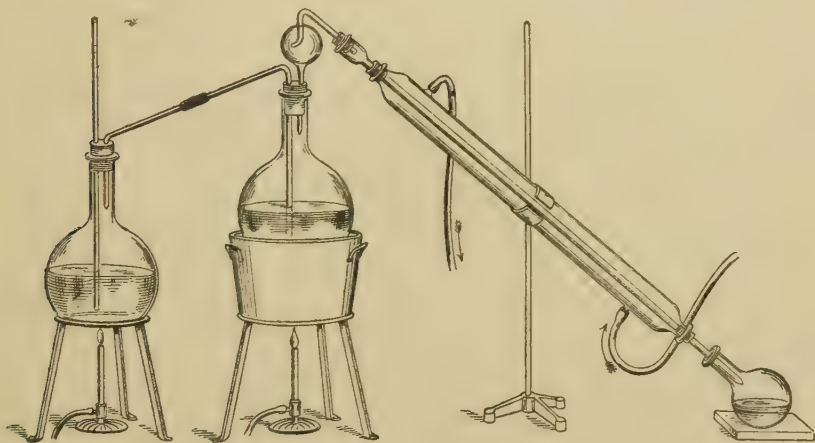


FIG. 3.—Apparatus for distilling in steam.

After the two distillations as described above are completed the contents of the flask are washed into a porcelain capsule, any excess of moisture from condensed steam removed by careful evaporation on the water-bath if deemed necessary, and the mixture then submitted to examination for the detection of inorganic or mineral poisons, nothing having been done in the above operations to destroy or volatilize them.

Examination for Mineral Poisons.—A number of processes have been devised for the extraction of mineral poisons in toxicologic investigations, in almost all of which the first procedure is the destruction, more or less complete, of the organic matter with which the poison is associated. One of the earliest methods suggested for this purpose was the actual combustion of the organic matter, either alone or after mixture with certain oxidizing agents like potassium nitrate, as practised by Orfila,¹ the father of modern toxicology. In these processes the

¹ Orfila, *Traité des poisons, ou toxicologie générale*, 1818, 2d ed., i, pp. 105, 207, etc.

material to be operated upon is properly dried, introduced into a crucible or other suitable vessel, and heated in contact with the air until the organic matter is completely burned away; the ash is then treated with acidulated water and the solution obtained tested for the presence of poison. This process has the advantage of simplicity and directness, and is still sometimes used, as, for instance, occasionally in testing urine for the presence of lead. Since, however, during the combustion a number of the most important mineral poisons, such as arsenic and mercury, are partially or wholly expelled and lost, the method has but limited application. The most generally useful processes are those in which chemical reagents are employed to remove the organic matter, and there are two chief methods at present in use: the first, that of Gautier, in which nitric and sulphuric acids are the destroying agents; and the second, that of Fresenius and Babo, in which the oxidizing effect of potassium chlorate when heated with hydrochloric acid is taken advantage of.

*Process of Gautier.*¹—This process, founded on the older methods of Danger and Flandin² (in which sulphuric acid alone was used) and of Fihol³ (in which a mixture of nitric and sulphuric acids was employed), has itself been modified more or less by Chittenden and Donaldson⁴ and by Chapuis.⁵ The method is best carried out as follows:

One hundred grams of the material to be examined are placed in a capacious casserole and treated with 30 gm. of nitric acid and moderately heated. After a time the mixture liquefies and assumes an orange hue, when it is removed from the heat and 6 gm. of sulphuric acid added. This usually causes a somewhat violent reaction, the mass becoming dark brown. It is again heated, either on a sand-bath or air-bath, until carbonization begins and the black mass commences to adhere to the side of the vessel; it is then removed from the source of heat, allowed to cool, and 10 or 15 gm. of nitric acid distributed over the mass drop by drop. It is again heated until white vapors have completely disappeared, when the mass is allowed to cool, pulverized, and boiled with two or three successive portions of water containing a sixth of its volume of hydrochloric acid. The mixture is filtered hot; in the carbonaceous mass left on the filter are to be found, in sparingly soluble combination, more or less of the silver, lead, bismuth, tin, barium, and strontium, which may have been present in the original material, while in the filtrate are all the other metals, excepting mercury, which in this process is either entirely or in great part lost by volatilization. The residue and the solution, being now free from organic matter, may be examined by the usual systematic procedures of qualitative analysis, if a complete search for all metals is to be made; or if but a single substance, such as arsenic, antimony, or lead, is sought, more direct and frequently

¹ *Annales de chimie et de physique*, 1876, fifth series, viii, p. 384.

² Danger et Flandin, *De l'arsenic*, Paris, 1841, p. 35; Flandin, *Traité des poisons*, 1846, i, p. 618.

³ *Thèses de la Faculté des Sciences de Paris*, 1848.

⁴ *American Chemical Journal*, 1880-81, ii, p. 235.

⁵ *Précis de toxicologie*, 3d ed., 1897, p. 150.

more delicate tests may be used, such as are described in connection with the individual poisons in the succeeding section.

The process as described above and the various modifications alluded to have, however, at least one serious inconvenience—the conversion of the organic material in the final stage into a solid carbonaceous mass from which the complete extraction of the metallic poison is extremely difficult. It is true that by pulverizing the material as directed and repeatedly treating it with hot acidulated water most of the mineral substances are almost entirely dissolved out. Traces, however, of even the more readily soluble substances are likely to be lost, and, as already stated, silver, lead, bismuth, tin, barium, and strontium remain to a greater or less extent in the carbonaceous residue, and can be tested for only with some difficulty. To remedy these defects Gautier¹ has more recently modified his method, using a larger amount of nitric acid and a lower degree of heat, in such a manner as to give, after the destruction of the organic matter, not a solid carbonaceous mass, but a liquid material from which the extraction of the various metallic poisons in their full amount is easy. This modification, like the original process, was devised especially for the detection of arsenic, and for this purpose it is particularly useful, but it may be advantageously employed for the separation of any of the metals except mercury, a part or even all of which may be lost, as in the original method.

Gautier's modified process, as practised by the writer, is as follows: On 100 gm. of the material there are poured from 30 to 60 gm. of pure nitric acid, the amount depending upon the character of the material operated on. One gram of sulphuric acid is now added and the mixture is heated, preferably on a water-bath at first, in a porcelain capsule until liquefaction is produced and the material becomes thick. It is then removed from the heat and not more than 8 or 10 gm. of pure sulphuric acid are added. The mixture is heated again rather strongly (care being taken, however, here and elsewhere, that the temperature shall not be high enough to produce carbonization), taken from the heat, and nitric acid poured over the material a little at a time until upon heating it to a point where thick vapors of sulphuric acid are given off there is left in the capsule a brown liquid practically uncarbonizable at the temperature at which sulphuric acid commences to boil. Usually about 50 gm. of nitric acid are required for this purpose, but sometimes a considerably larger amount is needed. In certain cases the destruction is difficult, and successive portions of nitric acid have to be added many times. When a point is finally reached where the nitric acid produces scarcely any further oxidizing effect, the acid is once more driven off by heat, the material allowed to cool, a little sulphuric acid added, and the small quantity of residual brown liquid poured with constant stirring into 600 to 700 c.c. of distilled water. The capsule is washed and the washings are added to the previous liquid. A finely subdivided brownish material falls to the bottom of the receptacle, and the supernatant liquid is more or less dark in color.

¹ Comptes rendus, 1899, cxxix, p. 936.

The liquid is filtered. The residue on the filter is to be tested, as in the original process, for silver, lead, bismuth, tin, barium, and strontium, while the filtrate is examined for traces of these (which may have passed more or less into solution) and for all the other metals.

Method of Gautier and Clausmann.—This newer method¹ of Gautier and his pupil avoids some of the disagreeable features of the other processes and yields rapid and reliable results for arsenic, although mercury and, possibly, a small portion of the lead are lost in the incineration. A portion of the suspected material is placed in a porcelain dish and heated in an oven to about 300° C., during which process it swells up and finally becomes pulverulent. By means of a pestle this dried residue is powdered and thoroughly mixed with 2 to 3 parts of quicklime (which is slaked with a little water) per 100 parts of dried weight of substance.² The mixture is ground fine and placed in a porcelain capsule with flat bottom and put in a small muffle heated to a moderate temperature, so that the bottom of the muffle just becomes faint red. The material, which at the beginning deflagrates a little, finally burns itself up slowly and easily. The destruction of such organic matter as stomach, liver, brain, etc., requires from two to four hours, the resulting product appearing in the form of porous, white or grayish cinders. Allow the material to cool, pulverize it, take it up with water faintly acidified with sulphuric acid, heat to boiling, filter, wash the residue on the filter with water, and concentrate the entire filtrate up to the point of liberation of white fumes. The acid residue may now be diluted with 8 to 10 volumes of water and used directly in the Marsh apparatus for determining arsenic, or other tests may be employed.

*Process of Fresenius and Babo.*³—This is much the most generally useful of the various methods that have been devised for the destruction of organic matter; it enables one to test for all mineral poisons, none being volatilized as in the process of Gautier. The procedure is based on the fact that when potassium chlorate and hydrochloric acid are heated together, chlorine and oxides of chlorine are abundantly evolved, which have an energetically destructive action on almost all forms of organic material. The process is founded on the older method of Jacquelin,⁴ in which a stream of chlorine conducted into the mixture was used for the same purpose.

In using the process, the suspected material is placed in a capacious evaporating dish or flask, mixed with about a third of its volume of concentrated hydrochloric acid, and gently heated on a water-bath;

¹ Compt. rend. Acad. des Sc., 1917, clxv, 11. Kohn-Abrest (Ibid., 1920, clxxii, 1179) advises the incineration with a mixture of magnesium oxid and magnesium nitrate as follows: To 100 gm. of ground material add 35 c.c. of a solution of magnesium nitrate (200 gm. per liter) and 1 gm. of magnesium oxid. Mix and heat to 250° C. to carbonize all organic material. Pulverize the residue and heat to 500° C. until all carbon is removed. Dissolve in 30 c.c. of 10 per cent. sulphuric acid and test in the usual manner.

² Fatty material or that very rich in phosphorous, such as brain, requires 3 parts of quicklime per 100, but, generally speaking, 2 parts per 100 suffices.

³ Annal. d. Chemie u. Pharmacie, 1844, xlix, p. 308.

⁴ Comptes rendus, 1843, xvi, p. 28.

from time to time pinches of pulverized potassium chlorate are added, and the volume of the mixture should be kept up by occasionally pouring in a little distilled water. The addition of the chlorate is continued until the mixture has a thin consistence, a uniform straw-yellow color, and no particles of organic matter remain suspended in the liquid excepting more or less fat, which in this process is only incompletely attacked. The mixture is now filtered and the insoluble material thoroughly washed with hot water. In the residue on the filter are to be found any silver that may have been present, in the form of the chlorid, and more or less of the lead, barium, and strontium, as sulphates, and these metals are to be tested for in this mixture. The amount of lead, barium, and strontium found in the residue depends on the quantity of sulphuric acid or sulphates present in the original substance or produced by oxidation from the sulphur of the organic compounds during the destruction of the latter. Barium and strontium are likely to be largely precipitated, but lead, unless in considerable amount, may pass entirely into solution, its sulphate being somewhat soluble in excess of warm hydrochloric acid, especially in the presence of chlorids of sodium and potassium. Barium has assumed decided toxicologic importance in recent years on account of its frequent employment in rat poisons and its use in x-ray examinations. If its presence is suspected it is better to make a direct test for it. (See p. 286.)

The filtrate, in which are to be found all the other metals, is to be moderately heated, and any excess of chlorine removed by passing through it a rapid stream of carbon dioxide. Sodium sulphite is then added in sufficient quantity to cause the liquid to smell strong of sulphur dioxide, and the gentle heating continued until the odor of the dioxide has disappeared. The object of using the sulphite (for which sulphurous acid may be substituted if more convenient) is to reduce any arsenic present from the form of arsenic acid, in which it exists in the liquid, to arsenous acid, in which state it is much more easily precipitated by hydrogen sulphide in the succeeding step of the process. If the liquid is exceedingly acid, it is well to neutralize it partially by the addition of sodium carbonate (for in the presence of too great acidity antimony and tin are likely to be imperfectly or even not at all precipitated by hydrogen sulphide), after which it is put in a flask, the temperature raised to and kept at about 70° C. (158° F.), and a washed stream of pure hydrogen sulphide from an automatic generator (Fig. 4) passed somewhat slowly through it for three or four hours. It is then allowed gradually to cool, the stream of hydrogen sulphide still continuing, and when entirely cold the gas is stopped, the flask well stoppered, and set aside in a warm place. At the end of twenty-four hours it is again heated to 70° C., treated with hydrogen sulphide exactly as before, the flask again stoppered, and once more set aside in a warm place for another twenty-four hours. If at the end of this time the liquid smells strongly of hydrogen sulphide, as is almost always the case if the operation has been properly conducted, the precipitation may be considered complete; but if there is little or no odor of the gas, the operation

as directed above must be repeated until the desired result is obtained. The contents of the flask are then thrown on a filter, and the precipitate well washed with water containing a little hydrogen sulphid in solution. The precipitate contains in the form of sulphids any mercury, bismuth, cadmium, copper, arsenic, antimony, tin, gold, and platinum, and a part or all of the lead, that may have been present in the original material, while in the filtrate are all the other metals excepting silver, and probably a part of the barium, and strontium, which, as we have seen, are more or less left in the residue after the destruction of organic



FIG. 4.—Apparatus for hydrogen sulphid.

matter by potassium chlorate. The precipitated sulphids and the filtrate may be examined by the usual methods of qualitative analysis; or if only one or two metals are in question, shorter and perhaps more delicate tests may be used, as suggested in connection with the Gautier process.

In this process of precipitating the heavy metals by means of hydrogen sulphid, it is important that the gas be free from traces of impurities, especially of arsenic, as an appreciable error might creep in if this point be overlooked. To secure such pure hydrogen sulphid the gas may be prepared in a generator by the use of known arsenic-free ferrous

sulphid and arsenic-free hydrochloric acid, or, if such material be not at hand, the gas, prepared from ordinary reagents, may be passed through a drying tube containing granulated calcium chlorid and then through a tube of about 8 mm. in diameter and 40 cm. long loosely filled with solid iodine mixed with glass wool and, finally, through a wash-bottle containing a solution of potassium sulphid or potassium iodid.¹

The process of Fresenius and Babo does not readily detect the presence of certain of the organic compounds of arsenic, several of which are largely used in medicine. For their detection consult p. 262.

*Process of Ogier.*²—Two objections have been urged to the process of Fresenius and Babo, namely, that small quantities of arsenic may be carried off as the volatile chlorid and lost, and that in projecting the chlorate into the acid mixture a considerable portion of the chlorine is

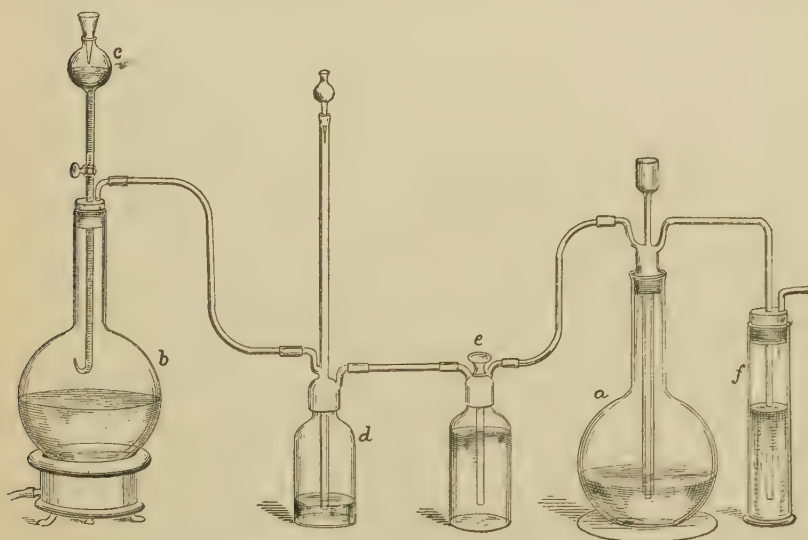


FIG. 5.—Apparatus for the destruction of organic matter (after Ogier).

evolved on the surface of the fluid and passes away without effecting destruction of any of the organic matter, necessitating the use of an excessive amount both of the chlorate and of the hydrochloric acid. To overcome these defects Ogier has modified the method of conducting the process by placing the material to be operated on in a flask, mixing it with the estimated amount of chlorate required for complete destruction of the organic matter (usually 1 part of the chlorate to 8 or 10 of the solids to be destroyed), and passing into the mixture a stream of hydrochloric acid gas liberated from the aqueous acid by allowing sulphuric acid slowly to drop into it. The operation is carried out in an apparatus shown in Fig. 5, in which *a* is the flask in which the organic

¹ See Jacobsen, Ber. d. d. chem. Ges., 1887, xx, 1999; and Pharmacopœia of the U. S., 9th Rev., 1916, p. 535.

² Le laboratoire de toxicologie, p. 41.

mixture and chlorate are placed, *b* the generator for producing the hydrochloric acid gas, *d* a bottle for washing the gas, and *f* a vessel in which the fumes given off from *a* are condensed so as to avoid all loss of arsenic; *e* is a bottle provided with a three-way stop-cock, so that in case the gas comes over too freely it may be diverted into the bottle and absorbed by the water in it. As the decomposition of the chlorate takes place in this process not on the surface of the mixture, but all through the mass, the organic matter, it is claimed, is more thoroughly and quickly destroyed and with a less expenditure of chemicals than in the original method; and as the operation is conducted in a closed vessel connected with a condenser, there should be no loss of arsenic. There are some inconveniences, however, connected with the process; it requires considerable care to keep the numerous parts of the apparatus perfectly clean, and, what is even more serious, when the hydrochloric acid gas comes in contact with the warm chlorate mixture, the chemical reaction under some conditions may become so vigorous as to fracture the flask and cause loss of material unless the process is conducted with constant attention. In spite of these drawbacks the method is to be recommended, especially when the quantity of poison present is believed to be small, since the amount of chemicals introduced in destroying the organic matter is reduced to a minimum and there is no loss of material.

*Process of Reinsch.*¹—In the processes given above for the extraction of mineral poisons the organic matter is destroyed as the first step. A very excellent method, however, was devised by Reinsch, in 1841, for the detection of certain of the poisonous metals without the previous destruction of organic substances. The process is one of great simplicity, and, if properly conducted, of thorough accuracy and considerable delicacy; it is applicable, however, to the detection of arsenic, mercury, and antimony only, but for rapid work, and especially for clinical use, it is of the greatest value. It is a qualitative test only, although an idea may be gained in a general way of the relative quantity of the poison present by the rapidity and intensity of thereactions obtained.

The process may advantageously be carried out as follows: The suspected material properly comminuted is put in a beaker, flask, or porcelain capsule, mixed with a quarter of its bulk of pure hydrochloric acid, water added, if necessary, to bring it to a thin consistence, and the mixture boiled for five or ten minutes, or until the substance under examination is thoroughly disintegrated. A piece of pure copper foil about $\frac{1}{2}$ inch long and $\frac{1}{4}$ inch wide, well polished by rubbing with fine emery paper, is now dropped in the mixture and the boiling continued a few minutes, the piece of foil being taken out at the end of each minute and inspected. For this purpose it is very convenient to hang the foil on a piece of platinum wire, but this is by no means essential. If at the end of ten minutes the foil has received no deposit, we may be sure that the above poisonous metals are either not present at all, or, at most, in only very minute proportion or that some interfering sub-

¹ Jour. für praktische Chemie, 1841, xxiv, p. 244.

stance, such as a nitrate, chlorate, or other oxidizing agent may be present; this latter point is to be especially borne in mind in the examination of embalming fluids. But, on the other hand, if the foil is coated it does not necessarily indicate that one of these substances is present, for certain other metals—gold, silver, platinum, palladium, tin, and, most important of all, bismuth—may also be deposited on the foil in an analogous manner. Arsenic and mercury in certain of their organic compounds are not readily detected by this process. (See p. 249.)

If a deposit is obtained, to determine whether one of the poisonous metals has produced it, several pieces of copper foil are treated in the same manner as the first, and when all have been coated they are washed with water, then with alcohol, and finally with ether, after which they are dried, placed in a small test-tube or sublimation tube, the diameter of which should not exceed $\frac{1}{4}$ inch, and gently heated in a small flame. If arsenic, mercury, or antimony is present, a sublimate will be produced in the colder part of the tube, and by examining this under the microscope, its nature can be determined, arsenic appearing in the form of octahedral crystals (see Fig. 33, p. 224), mercury as metallic globules (see Fig. 29, p. 187), and antimony either in the form of amorphous granules or as needle-shaped crystals. Occasionally antimony produces a sublimate of octahedral crystals somewhat resembling those of arsenic,¹ but distinguishable from the latter by the fact that they are volatilized by the application of a high degree of heat only (between 700° and 800° C.), while those of arsenic are sublimed at a comparatively low temperature (about 200° C.). Neither bismuth nor any of the other metals mentioned above produces any sublimate if, as directed, a gentle heat is used, and they can be distinguished as a class, therefore, from the poisonous metals very easily.

If after introducing the coated foil into the sublimation tube the latter, as recommended by Wormley,² is drawn out to a capillary tube and the sublimation then effected, the sublimate can be very much more easily examined under the microscope, and the results obtained are considerably more exact. Or, if a subliming cell, as recommended by the National Health Society of England³ and as described on p. 224 of this volume, is used, the test is still more delicate.

It is highly important that the subliming tube be thoroughly clean and dry, and the foil free from all grease. Failure to observe these conditions may produce confusing and uncertain results. In manipulating the foil after it has been washed with ether it should preferably not be touched with the finger, but handled with forceps, to avoid imparting any trace of oil to it.

Sometimes, in applying the test, the copper foil becomes more or less stained by the action of the sulphur and possibly of some other normal constituents of the organic matter operated on; but upon heating

¹ Wormley, *Amer. Jour. Med. Sci.*, 1877, n. s., lxxiv, p. 399.

² Wormley, *Micro-Chemistry of Poisons*, New York, 1869, p. 271.

³ *British Med. Jour.*, June 23, 1883, p. 1220.

the foil thus coated in the subliming tube, either no sublimate is obtained, or an amorphous one, which can very easily be distinguished under the microscope from the sublimates produced by the poisonous metals.

It should be added that sulphur in certain inorganic compounds, such as sulphids, sulphurous acid, and thiosulphates, also produces a deposit on the foil, and the same is true of the compounds of selenium and tellurium. These bodies, however, especially the two last, are rarely present in mixtures submitted to the test, and, moreover, they may be readily differentiated from the poisonous metals by their behavior when the coated foil is heated in a tube. All three under this treatment give slight sublimates which condense but a short distance from the foil; that from sulphur is yellowish and either amorphous or in acicular crystals, and those from selenium and tellurium appear in colorless needle-shaped or cubical crystals which arrange themselves in characteristic fern-like masses.

It is very desirable, whenever possible, to confirm the character of the sublimate by other tests, and this can be accomplished easily as follows: A small crystal of iodine is placed in the tube, which is then sealed with wax and put aside in a warm place for several hours, when, if mercury is present, it will be converted into mercuric iodide and the sublimate will assume the bright red color of that compound. If the result of this test is negative, the iodine is removed, the portion of the tube containing the sublimate is cut off with a file and placed in a test-tube; distilled water is added and boiled, by which arsenous oxide, if present, is dissolved out, and may be tested for in the solution by the action of hydrogen sulphide or of other liquid tests for arsenic. If the test for arsenic is also negative, the piece of glass tubing containing the sublimate should be boiled with a solution of tartaric acid, which dissolves oxide of antimony, and its presence in the liquid may be demonstrated by hydrogen sulphide or by other tests for antimony. It should not be forgotten, however, that more than one of the metals may be present, in which case we get, both in the appearance of the sublimate under the microscope and in the subsequent identifying reactions, results that characterize the different metals present.

A very important point in connection with the test is that the production of a coating on the copper foil must never be taken as proof of the presence in the mixture under examination of a poisonous metal; subsequent sublimation, and the examination of the sublimate under the microscope, must invariably be practised before any conclusion should be drawn.¹

Detection of Organic Poisons.—Laying aside volatile organic poisons, which have already been considered, organic compounds of toxicologic interest may with few exceptions be divided into four groups, as follows: (1) alkaloids and other basic substances; (2) glucosids and other neutral principles; (3) acids; (4) oils, gums, resins.

¹ For further discussion of this valuable test see pages 195 and 223 in the section on Inorganic Poisons.

Of the above the most important from a toxicologic standpoint are the alkaloids, and the earliest systematic processes for the detection of organic poisons were devised for their extraction; by a modification, however, of these processes most or all bodies belonging to the other classes may also be detected, if discoverable at all. Stas, of Belgium, was the first to introduce a satisfactory method for the extraction of alkaloids for toxicologic purposes, the process having been invented for the detection of nicotin in the body of M. Fougnyes, who was poisoned with that alkaloid in 1850 by his brother-in-law, Count Bocarmé. His method, which may be said to be the origin of all general processes for the detection of organic poisons, is, in brief, as follows:

*Process of Stas.*¹—The finely divided material is mixed with two or three times its volume of strong alcohol acidulated with tartaric or oxalic acid, gently heated—the temperature never exceeding 75° C. (167° F.)—filtered when cold, and the filtrate evaporated in a vacuum or in a current of air, at a temperature not above 35° C. (95° F.). If any insoluble matter separates during evaporation, the liquid is again filtered, evaporated still further in a vacuum, the residue extracted with absolute alcohol, and the solution thus obtained evaporated at a low temperature. The residue is taken up with a small quantity of water, filtered, the filtrate rendered alkaline with sodium bicarbonate and agitated at once with several times its volume of ether; the latter is drawn off and allowed to evaporate spontaneously, when any alkaloid which may have been present in the substance under examination is left behind.

Numerous modifications of Stas' method have been introduced.

*Otto*² suggested agitating the final acid liquid, before adding sodium bicarbonate, with ether, which removes coloring-matter, glucosids, and many other non-alkaloid substances, which may be recovered and tested upon evaporating the ether. This modification, commonly known as the *Stas-Otto process*, is greatly to be preferred to the original as furnishing the alkaloid in a much purer state.

*Rodgers and Girdwood*³ extracted with dilute hydrochloric acid, and suggested the use of chloroform instead of ether. While their process was devised particularly for the isolation of strychnin, it is applicable for the detection of most of the alkaloids, and has the advantage over the original Stas method, that chloroform is a much better solvent of most alkaloids than ether is, a fact that has justly caused it largely to supplant the latter in general alkaloid extraction.

*Uslar and Erdmann*⁴ also extracted the material under examination with water slightly acidified with hydrochloric acid, alkalized the filtered liquid with ammonium hydroxid, and shook out with hot amyl alcohol, in which alkaloids are freely soluble, and which has the advantage over ether and chloroform of readily dissolving out morphin, which is sparingly soluble in the other two liquids.

¹ Bulletin de l'Acad. de Méd. de Belgique, 1851, xi, p. 304.

² Annal. d. Chem. u. Pharm., 1856, c, p. 44.

³ Lancet, June 28, 1856, i, 718; Pharm. Jour. and Trans., 1856, xvi, first series, p. 497.

⁴ Annal. d. Chem. u. Pharm., 1861, cxx, p. 121.

All the above and a number of other modifications of the Stas process are founded on the following general principles: (a) Water or alcohol, acidulated with acetic, tartaric, hydrochloric, or other acid, extracts from complex mixtures any alkaloids present in the form of readily soluble salts, along with glucosids and most other organic bodies of toxicologic interest, together with many impurities. Ligneous fibers, insoluble proteins, starch, fats, resins, and many other similar substances are wholly or chiefly left undissolved and are separated by filtration. (b) If the solution thus obtained after expelling alcohol (if any has been used) is agitated with ether, chloroform, or other analogous immiscible liquids, glucosids, acids, etc., are dissolved out, and may be recovered for examination by evaporation of the immiscible solvent, while the alkaloid salts are left behind in the acid aqueous solution. (c) If the latter is rendered alkaline by ammonium hydroxid, potassium hydroxid, sodium carbonate, or other similar body, any alkaloid salts present are decomposed, the acid being abstracted, and the free alkaloids, which, as a rule, are sparingly soluble in water, are set at liberty and in part thrown out of solution. (d) If this mixture is now agitated with ether, chloroform, or other similar immiscible fluid, any alkaloids present pass almost wholly into solution in the immiscible solvent, and if the latter is drawn off and evaporated, the alkaloids are left behind in the residue, and may be identified by appropriate tests, particularly after purification.

*Process of Dragendorff.*¹—Following these general principles, and, in addition, taking advantage of the different solvent powers of various immiscible liquids upon alkaloids and other organic bodies when in acid and in alkaline solutions, Dragendorff has devised an elaborate and valuable process not only for the extraction of nearly all non-volatile organic compounds of toxicologic interest, but also for their separation into a number of groups to facilitate their identification. In cases of suspected poisoning in which a complete examination is to be made, and particularly in those in which no clue is afforded to the poison present, this method or one of its modifications is of the greatest utility. It is, however, somewhat long and complicated, and when only one or two organic substances are to be looked for it may very advantageously be materially changed and much more direct methods employed, such as are given later on in connection with the individual poisons.

The process is carried out as follows: The finely divided material is digested for a number of hours with water acidulated with sulphuric acid at a temperature of 40° C. The solid material is pressed and again extracted with dilute acid and pressed as before. The united fluids obtained by expression are filtered and the filtrate evaporated at a gentle heat to a syrupy consistence, when it is mixed with several times its volume of alcohol to precipitate proteins, the mixture digested for several hours at a moderate heat, allowed to cool, and filtered. The filtrate is freed from alcohol by gentle heat, the aqueous residue diluted with water if necessary, and clarified by filtration. The acid liquid thus

¹ *Ermittelung der Giften*, 1895, p. 149.

obtained is shaken out with petroleum ether in several successive portions until nothing further is removed by it, as is shown by leaving no residue upon evaporation. The liquid while still acid is then similarly extracted first with benzene and then with chloroform, after which the fluid is shaken with petroleum ether in order to remove traces of chloroform, and ammonia is added to alkaline reaction.

The alkaline liquid is now extracted successively with petroleum ether, benzene, chloroform, and amyl-alcohol, after which the fluid is evaporated to dryness with the addition of powdered glass, and the finely divided residue is extracted with chloroform.

By evaporating the several immiscible solvents used above, residues are obtained containing the various substances extracted by them, which according to Dragendorff, are chiefly as follows:

Petroleum Ether from the Acid Solution.—Piperin, picric acid, salicylic acid, benzoic acid, camphor and ethereal oils, capsin, and the esters of salicylic and benzoic acids with guaiacol, naphthol, and cresol.

Benzene from the Acid Solution.—Caffein, geissospermin, traces of veratrin and hydrastin, piperin, cantharidin, anemonin, santolin, caryophyllin, cascarillin, cubebin, aloëtin, elaterin, colocynthin, populin, digitalin, strophanthin, picric, benzoic, and salicylic acids, traces of hydroquinon and resorcin, and salophen.

Chloroform from the Acid Solution.—Theobromin, colchicin, papaverin, narcein, hydrastin, cinchonin and cinchonidin, jervin, aspidospermin and quebrachin, acetanilid, picrotoxin, colocynthin, esculin, and gelsemic acid.

Petroleum Ether from the Alkaline Solution.—Coniïn, nicotin, spartein, lobelin, pyridin, anilin, kairin, thallin, phenocoll, antipyrin, aconitin, delphinin, and traces of strychnin, brucin, gelsemin, emetin, quinin, veratrin, and the alkaloids of quebracho and of geissospermum.

Benzene from the Alkaline Solution.—Strychnin, brucin, gelsemin, emetin, quinin, veratrin, and the alkaloids of quebracho and geissospermum (traces of which, as shown above, have already been removed by petroleum ether from the alkaline solution); cocain, atropin, hyoscyamin, hyoscin, physostigmin, eserin, pilocarpin, narcotin, codein, thebain, apomorphin, antipyrin, and thallin.

Chloroform from the Alkaline Solution.—Berberin, what is left of the cinchona alkaloids, of papaverin, and of narcein, and slight traces of morphin.

Amyl-alcohol from the Alkaline Solution.—Morphin, solanin, salicin, and traces that may have been left of certain other bodies, such as narcein, cystin, saponin, etc.

Curarin is not removed by any of the above solvents, but is extracted from the residue left after evaporating the fluid with powdered glass by treatment with chloroform.

Each of the above residues should be examined for the various substances which may be present in it by identifying tests such as are fully described in connection with the different poisons. The residues are,

however, rarely pure enough to be tested at once, but generally require purification by solution in acidulated water, and re-extraction by the appropriate immiscible solvents, and this process of purification sometimes has to be repeated a number of times.

In this and in all other processes in which shaking out with immiscible solvents is practised, emulsions of the latter with the aqueous liquid not infrequently are produced and greatly embarrass the procedure. From these emulsions the immiscible solvent separates with great tardiness, hours and even days sometimes passing before the separation is complete. To overcome such emulsions many suggestions have been offered, such as adding an additional amount of the solvent, gently heating the mixture in a water-bath, slowly stirring with a glass rod, and submitting to the action of a centrifuge. While one or all of these devices may often be used with advantage, the most satisfactory method is, as far as possible, to prevent the formation of the emulsion, and this can usually be accomplished by care in agitating the mixture. If, upon adding the immiscible solvent and shaking gently, it is seen that an emulsion is likely to follow, the agitation



FIG. 6.—Separating funnel.

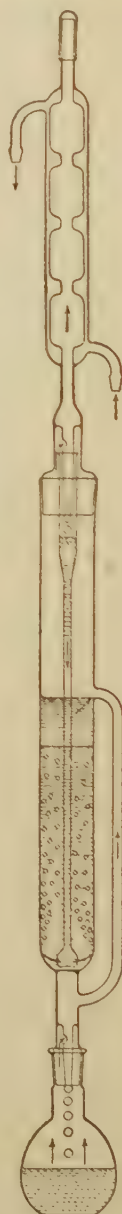


FIG. 7.—Perforator for liquids lighter than water.

should be discontinued at once, the solvent allowed to separate, and after it has been drawn off a fresh portion poured in and again gently

shaken. After the first or second extraction there is less likelihood of a persistent emulsion forming, although this is not invariably the case. In thus using gentle agitation only it is necessary to depend on repeated portions of the immiscible solvent to make a complete extraction; but the saving in time and patience, as well as the greater accuracy of the results obtained, much more than compensate for this slight disadvantage.

In this, as in all other processes of shaking out with immiscible solvents, a separating funnel (see Fig. 6) is of particular value, but a test-tube or flask may be used and the two layers of liquid separated from each other by the convenient device introduced by Prescott¹ (Fig. 9). As will be seen by referring to the figure, this consists of a doubly perforated stopper provided with two glass tubes, one of which passes only just through the stopper, while the



FIG. 8.—Soxhlet extraction apparatus.

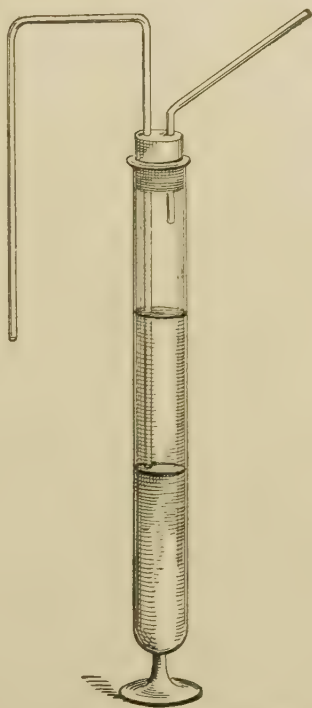


FIG. 9.—Prescott separating device.

other is much longer and may be drawn up and down to suit different levels of the liquids. The method of using it will be evident from an inspection of the illustration.

Instead of shaking out the various fluids with immiscible solvents, as described above in connection with the Stas, Dragendorff, and other similar processes, quicker and usually more perfect results may be obtained by the use of a perforator, in which the immiscible extracting solvent, such as ether or chloroform, is automatically and continuously carried through the aqueous liquid and the extraction is rapidly effected

¹ Organic Analysis, p. 36.

(Fig. 7). Two forms of perforators are necessary, one when liquids lighter than water, like ether, and the other when liquids heavier than water, like chloroform, are used.

When but a small amount of stomach contents, vomitus, or other material is available for examination for organic poisons the extraction by means of a Soxhlet's extraction apparatus (one form of which is shown in Fig. 8) is sometimes very useful. The material for examination must first be thoroughly dried, preferably after mixture with sand or other inert material. It is then introduced into the apparatus and extracted with ether, chloroform, or other appropriate solvent with or without the combined action of acids or alkalies.

The Author's (Haines) Modification of the Dragendorff Process.—Dragendorff's process has two serious drawbacks: First, the use of so strong and disintegrating an acid as sulphuric in extracting the alkaloids from the tissues causes much foreign matter to go into solution and produces many new soluble compounds which still further contaminate the resulting extract, greatly to the disadvantage of the subsequent procedures. Second, on account of the presence of these many impurities the volume of the fluid when subjected to the shaking-out process is usually so considerable that the treatment with immiscible solvents requires the use of a large amount of the latter, and this impairs greatly the sharpness of division into groups, which is one of the chief merits claimed for the method.

In order to overcome these objections the author has modified the process as described below. As will be noted, sulphuric acid is replaced by tartaric or other vegetable acid, the first extraction is made with alcohol instead of with water, and subsequently the extract is purified repeatedly by treatment with an excess of strong alcohol. By these procedures the final fluid for shaking out is freed entirely from all protein material and many other impurities, and is reduced to a comparatively small volume. When the immiscible solvents are applied, much less time and material are necessary, emulsions (such as embarrass the original Dragendorff process greatly) rarely occur, and the extracted alkaloids and glucosids are of far greater purity and their division into groups much sharper.

In conducting the process the material under examination is finely divided, placed in a capacious flask, and treated with three times its volume of 50 per cent. alcohol acidulated with acetic or tartaric acid. The mixture is heated on a water-bath to a temperature not exceeding 50° C. (122° F.) for an hour or two, and then filtered, the insoluble residue being thoroughly washed with dilute alcohol, strongly pressed, again digested with acidulated spirit, and the liquid filtered and residue pressed as before, the operation being repeated a number of times until thorough extraction is accomplished. The united filtrates and washings are evaporated at a moderate temperature, preferably not exceeding 60° C. (140° F.), to the consistence of a syrup, and, while it is still warm, three or four volumes of 90 per cent. alcohol are very slowly stirred in. The mixture is allowed to digest in a warm place with frequent agitation

for at least an hour, when the liquid is filtered from the insoluble residue and the latter digested and washed repeatedly with warm slightly acidulated alcohol. The filtrate and washings are again evaporated to a syrupy consistence, as before described, and when cold taken up by the very gradual addition, with constant stirring, of three or four volumes of absolute alcohol; the mixture is filtered, and the insoluble residue thoroughly digested and washed with slightly acidulated absolute alcohol. The filtrate should now be tested by adding to a small portion of it in a test-tube an equal quantity of absolute alcohol; if a precipitate is produced, it is evidence that proteins and other coagulable foreign matter have not been completely removed, and the liquid must be evaporated to a small bulk as before and again treated with a large excess of absolute alcohol; and this process must be repeated, if necessary, until all coagulable material has been eliminated. But if the alcohol occasions no deposit, the filtrate and washings are reduced by evaporation to a syrupy liquid, which when cold is taken up with two or three volumes of water containing a few drops of sulphuric acid. The mixture is filtered, the insoluble residue well washed with water, and the united filtrate and washings shaken out with repeated portions of petroleum ether until nothing further is extracted.

If a complete examination is to be made, the aqueous liquid is now agitated in turn with the various other immiscible solvents of the Dragendorff process. For this treatment it is well fitted, since, as before stated, all proteins and a large number of other foreign matters have been separated in the preparatory operation. It should not be large in bulk, and should not emulsionize easily upon being shaken out with the different immiscible solvents, if the various steps in the above process have been carefully carried out.

In case only one or two specific poisons are to be looked for, and a general examination for alkaloids is unnecessary, the acid liquid after being purified by treatment with petroleum ether may often with advantage be tested directly for the suspected substances. If, for instance, strychnin is to be examined for, the liquid is alkalinized, shaken out with chloroform, and the latter evaporated, when the alkaloid, in a condition of greater or less purity, is left as a residue; if morphin is sought, the alkalinized liquid is extracted with amyl-alcohol, acetic ether, or hot chloroform; and so on for the other individual poisons.

The use of strong alcohol for the initial extraction, as is generally recommended, is inadvisable; it produces an abundant, firm coagulum of protein material which is practically certain to occlude more or less of the alkaloids present and retain them in spite of repeated washings. This is especially true if an organ like the liver or kidney is operated on; but even in the case of softer material, like the contents of the stomach or of the intestine, particularly if a large amount of undigested food is present, a part of the alkaloid is almost sure to resist extraction. By using, however, as directed above, gradually increasing strengths of alcohol, the precipitation of the proteins is accomplished fractionally and

the danger of loss is reduced to a minimum. The step in which there is the greatest possibility of loss is the first extraction, and the use even of dilute alcohol is sometimes prejudicial. This is particularly the case when the amount of poison present is small and the material to be operated on bulky and of firm consistence. In this event the first extraction should be made with acidulated water, repeatedly applied, and the filtrate after evaporation to a small bulk treated with dilute alcohol, the remainder of the process being carried on as already directed.

The evaporation of considerable volumes of aqueous and alcoholic liquids at a moderate temperature, as contemplated in this and other

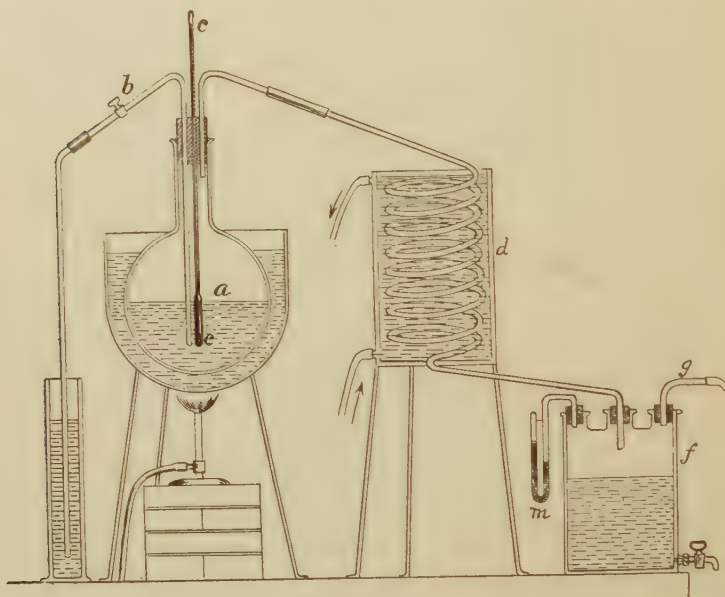


FIG. 10.—Apparatus for evaporating under reduced pressure (Ogier). The liquid is placed in the flask *a*, heated in a water-bath; the temperature is indicated by the thermometer *c*. Tube *b*, provided with a stop-cock, is for admission of small bubbles of air to facilitate boiling; the tube also serves to introduce fresh quantities of liquid without opening the apparatus; *d* is a worm surrounded by running water; *f* is a bottle to receive the condensed alcohol; tube *g* communicates with a vacuum pump; the pressure is indicated by the manometer, *m*.

methods, is often exceedingly tedious; it may be hastened, however, very advantageously by conducting the process under reduced pressure. An excellent apparatus for accomplishing this is described by Ogier,¹ and is shown slightly modified in Fig. 10.

Method of Ipsen.—This process² was suggested by Ipsen as one for the separation of strychnin, but may be used as a general one for the alkaloids, varying the immiscible solvent to suit the solubility of the

¹ *Traité de chimie toxicologique*, 1899, p. 508.

² *Vrtljschr. f. ger. Med.*, 1912, 3f. xliii, Supp. II, 273. See, also, Ipsen, *Ibid.*, 1892, 3f. iv, 15 and 1895, 3f. x, 1; Bakemin and Majore, *Gaz. chim. ital.*, 1906, xxxvi, 227; Molitoris, *Vrtljschr. f. ger. Med.*, 1906, 3f. xxxi, 329; Peset y Alexandre, *Rev. med. de Sevilla*, 1911, lvii, 5.

special alkaloid sought. The method is as follows: The finely divided material is extracted on the water-bath at a moderate temperature with distilled water slightly acidulated with acetic acid. The extraction is repeated several times, filtering the extract and pressing out the material by means of a hand press at each filtration. It is also advisable to grind up the material at each extraction with a pestle in order to facilitate the extraction. The combined filtrates are evaporated to a syrupy consistence and treated with absolute alcohol added in small amounts at a time with constant stirring. The alcoholic solution is filtered and the alcohol distilled off, when the acid residue is taken up with a small amount of water. Add to this watery extract a solution of lead acetate as long as a precipitate forms, filter, wash the residue with water, and precipitate the lead from the filtrate by means of hydrogen sulphid. Filter off the lead sulphid and evaporate the filtrate once more to a syrup. Treat this syrup with absolute alcohol as before and filter, washing the residue with absolute alcohol. Again distil off the alcohol and take up the residue with water, filtering to obtain a clear solution. Shake out this acid aqueous extract with chloroform, alkalinize with sodium or ammonium hydroxid, and again shake out with chloroform. This last chloroform extract will contain the alkaloids. To this chloroform extract add a few drops of dilute sulphuric or acetic acid and allow the residue to crystallize in the form of the sulphate or acetate in the desiccator.

Separation of Alkaloids from Residual Fat.—In all of the above processes for separating alkaloids, during the evaporation of alcoholic solution and also when the residue from an alcoholic extraction is treated with acidulated water, there is nearly always a considerable separation of fatty material which has a tendency to retain more or less of the alkaloid, and unless means are resorted to for recovering the latter a decided loss may occur, amounting in some cases to nearly, if not quite, half of the total amount present. A number of methods have been suggested to avoid this loss. Repeated agitation with warm acidulated water may be resorted to; but perhaps the best means is that recommended by Noyes,¹ which consists in dissolving the oily residue in purified petroleum ether, adding very dilute sulphuric acid, and thoroughly mixing the two by passing them through a filter with the aid of a pump. The acid solution, which contains now practically all the alkaloid, is allowed to separate and added to the other portion of the aqueous extract.

Loss in Extraction.—It should be constantly borne in mind in extracting organic poisons that even with the greatest care some loss is sure to occur in practically every operation. This loss is perhaps greatest in the use of immiscible solvents. Every organic poison, whether alkaloid or otherwise, and if alkaloid whether in the state of the free base or of a salt is invariably more or less soluble in every menstruum employed in purifying the material. It is commonly assumed that in shaking out an acid solution with ether, chloroform, or other immiscible solvent all

¹ Jour. Amer. Chem. Soc., 1894, xvi, p. 109.

of the alkaloid salt remains in the aqueous solution; but this is far from true, some of the alkaloid salt always being taken up by the immiscible liquid used. In this way a serious loss of the poison may occur, and if the amount originally present is small there may be even a complete failure to detect it, the losses being so considerable. It is indispensable, therefore, that the utmost care be employed at every step, no procedure being entered upon until it has been fully considered, especially from the standpoint of possible loss. On account of inevitable losses in the extraction of organic poisons the author believes that quantitative determinations of them rarely give more than approximate results.¹

Separation of Ptomaines.—One of the most serious obstacles in the way of the perfect identification of alkaloids when extracted by the above processes is their possible contamination with ptomaines and other products of putrefactive decomposition. While this fact applies to all of the alkaloids more or less, it is particularly true of morphin, whose reactions in certain respects are closely simulated by those of some of the protein decomposition products. For strychnin, fortunately, we have a means in the use of warm concentrated sulphuric acid of getting rid of such extraneous substances; but this method is not practicable with morphin or with most of the other alkaloids. Many methods have been suggested for the elimination of these bodies; the following is a process which I have used with much advantage, and which generally gives satisfactory results. It depends on the fact that ptomaines and other products of protein decomposition when exposed to the air, especially if gently heated, slowly take up oxygen, resinify, and otherwise change so as to lose their identity; they become in part difficultly soluble in acidulated water, and in part removable from an acid fluid by repeated shaking with ether, while most alkaloids under this treatment undergo comparatively little or no decomposition.

The process is carried out as follows: The ether, chloroform, amyl-alcohol, or other immiscible solvent used in extracting the alkaloid is allowed to evaporate in a capacious watch-glass or flat-bottomed evaporating-dish so that the residue may present a large surface to the action of the air. After the solvent has evaporated, the residue is gently heated on a water-bath for an hour or two, and afterward put aside in a warm place for two or three days. The more or less resinified material is then extracted with very dilute sulphuric acid, the solution filtered, the acid filtrate shaken repeatedly with ether, alkalized, and shaken out with the appropriate immiscible solvent. The latter is allowed to evaporate, and if the residue is still found to be impure, the treatment above described is repeated one or more times, sometimes many repetitions being necessary. Eventually, if care is taken with all the details of the process, the alkaloid is usually obtained in a practically pure condition.

¹ The presence of caffen in the stomach or other organs tested may occasion a serious error in quantitative determinations of alkaloids, as has been shown by Haines and Webster, and as is explained more in detail on page 585 in the section on Alkaloidal Poisons.

The method, however, entails the loss of more or less material, and this should be remembered in quantitative testing. But for qualitative work this is usually of little moment, as a small amount of a pure alkaloid is greatly to be preferred to a large quantity of impure—the former yielding delicate and characteristic reactions, while the latter often gives entirely unreliable results.¹

Another method of extracting alkaloids which is of particular importance in this connection is the—

*Process of Kippenberger.*²—To isolate alkaloids and glucosids, and especially to separate them from ptomains and other products of putrefaction, this process is possessed of much merit. The method is based on the fact that the alkaloids and glucosids are generally soluble in a mixture of tannic acid and glycerin, while proteins and putrefactive substances in general are usually rendered insoluble by it. The process is as follows:

The finely subdivided material is macerated for two days at 40° C. in a 10 per cent. solution of tannic acid in glycerin. The mass is then placed in a cloth bag and the fluid portion thoroughly squeezed out, preferably by means of a press; the liquid thus obtained is heated to 50° C., cooled, and filtered. The filtrate is shaken with petroleum ether to remove fats, and is then heated on a water-bath to expel a small amount of petroleum ether left in solution. The liquid is now agitated thoroughly with successive portions of chloroform, first while still acid, and then after being alkalized with potassium hydroxid. Sodium or potassium bicarbonate is next added to convert any excess of alkaline hydroxid into carbonate, and the mixture extracted with chloroform containing about 10 per cent. of alcohol. The solution is then saturated with sodium chlorid and shaken out with chloroform containing about 15 per cent. of ether.

The *petroleum ether* in the above process extracts traces of jervin and veratroidin, together with fat.

The *chloroform* extracts from the *acid solution* aconitin, canthardin, colchicin, digitalin, geissospermin, jervin, narcotin, papaverin, picrotoxin, and traces of brucin, delphinin, narcein, strychnin, and veratrin.

The *chloroform* removes from the *alkaline solution* apomorphin, atropin, brucin, codein, coniin, emetin, nicotin, pilocarpin, spartein, strychnin, veratrin, and any narcotin and papaverin left from the preceding operation.

The *alcohol-chloroform* extracts morphin and narcein, and the *ether-chloroform* removes strophanthin.

Upon evaporating either of the above immiscible solvents the substances it has extracted from the liquid are left as a residue to be examined by appropriate tests.

¹See Ionescu (Bul. soc. chim. România, 1921, ii, 82; Chem. Abstracts, 1921, xv, 1116) for a discussion of the differences in the action of oxidases and other ferments on ptomains and on alkaloids. He believes that the oxidation by means of hemoglobin can be used in practice to distinguish between these bodies, the hemoglobin having a marked effect on ptomains, but none upon alkaloids.

²Zeitschr. f. anal. Chemie, 1895, xxxiv, p. 294.

In order to avoid some of the inconveniences attending the use of glycerin in the above process, Kippenberger¹ has more recently suggested the use of acetone in conjunction with tannic acid. To the solution thus obtained a small quantity of glycerin and a little dilute hydrochloric acid are added, the acetone evaporated off, and the resulting aqueous solution is extracted by immiscible solvents, as described above.

Separation of Poisons by Dialysis.—Taking advantage of the discovery by Graham of the difference in diffusibility through porous membranes of crystalline and colloid bodies, many poisons of a crystalline nature may be separated from contaminating organic matter by the process of dialysis. When first suggested for this purpose it was believed that it would yield results of great value, but practical experience has scarcely borne out these expectations. At times it may be used with considerable profit in selected cases or in preliminary testing, but, as a rule, it cannot compare in value with the methods already given for the separation of either mineral or organic poisons. Since in using the process, however, nothing is done to the material to change

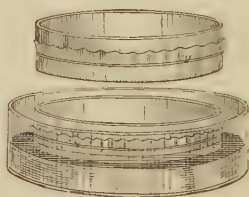


FIG. 11.—Graham's apparatus for the application of dialysis.

its constituents chemically, the poison is procured in practically the same condition in which it existed in the matter submitted to examination. In some instances this is a point of no small moment in toxicologic investigation; it is occasionally of great importance, for the purpose of identification, to establish the exact form in which a poison has been administered, or in which it exists in the stomach contents or vomited matter, and when such is the case dialysis may be of much service.

The usual method of performing the operation is to place the material, finely subdivided and brought to a thin consistence by the addition of water if necessary, in a dialyzing vessel, which is supported in a dish of pure water for twenty-four hours with an even level of the two liquids. At the end of that time the crystalline constituents of the material, such as arsenic, tartar emetic, oxalic acid, and the various alkaloids, are generally found, in part at least, in the outer fluid, and may be tested for directly by the use of appropriate reagents or may be recovered for identification by evaporation. In the case of alkaloids the liquid may be shaken out with immiscible solvents for the purpose of more complete purification. If the amount of poison in the material, however, is small,

¹ *Zeitschr. f. anal. Chemie*, 1900, xxxix, p. 627.

or if it has entered into firm protein combination, so little of it may pass into the outer fluid as to give unsatisfactory results.

The dialyzer above spoken of may be made by tying a piece of thoroughly sound parchment-paper over a hoop of wood or gutta-percha, or over the end of a glass jar or stout beaker from which the bottom has been removed. It may be made of any size suitable for the amount of material used, but it is well to have as large a surface of parchment-paper as possible to facilitate the operation. Usually a diameter of 6 to 8 inches (15 to 20 cm.) and a height of 2 to 3 inches (5 to 8 cm.) will serve the purpose (Fig. 11).

In recent years Abel, Rowntree, and Turner¹ have introduced a method, which may be referred to as "vividiffusion," which permits of the detection of poisons actually circulating in the blood of the patient during life. The principle of the method consists in connecting an artery by a cannula to an apparatus made of celloidin or other dialyzing membrane, in the form of tubes, immersed in a saline solution or serum (this outer fluid may be of water, but this leads quickly to hemolysis of the red cells, which is very undesirable), and providing for the return of the blood to the body by another cannula attached to a vein. The tubes and cannulæ are filled completely before attachment with a saline solution which approximates in composition to the salt content of the serum. This is displaced into the body by the inflow of blood, when the circulation in the apparatus is established. The blood leaving the artery flows through a perfectly closed system and returns to the body within a minute or two without being exposed to contact with the air or any chance of infection, while the diffusible substances which it contains can pass out, more or less rapidly through the walls of the tubes. For the details of the method as well as for a description of the apparatus the original article must be consulted.

Cremation in its Relation to the Detection of Poisons.—The question occasionally arises as to whether after the cremation of a body it is possible still to detect the presence of poisons which may have been administered to the deceased. If we consider the conditions under which cremation is now practised (see Cremation, page 883, in article on Destruction of the Body, etc.) it is quite evident that all organic and volatile poisons would be completely destroyed or expelled during the burning of the body, and as a consequence no poisonous substances could possibly remain in the ashes excepting perhaps small amounts of lead and copper and traces of arsenic, which very likely might pass through the highly heated furnace without complete volatilization. It would be entirely useless to examine the remains from cremation for any of the alkaloids, glucosids, or other poisonous organic substances, or for mercury, antimony, zinc, and the other poisonous metals which, like these, are at least fairly readily volatilized under the conditions existing. In the case of arsenic, too, the poison would be almost completely, or pos-

¹ Jour. Pharmacol. and Exp. Ther., 1913-14, v, 275 and 611. See, also, Hess and McGuigan, *Ibid.*, 1914, vi, 45; Love, *Med. Record*, 1920, xcvi, 649; Van der Heyde and Morse, *Jour. Lab. and Clin. Med.*, 1921, vi, 520.

sibly wholly, expelled according to theoretic considerations, and this has been found practically to be the case.¹

Relation of Embalming to Toxicologic Examinations.²—In former years compounds of arsenic and mercury were largely used by embalmers for the preservation of the body after death, and as a consequence many difficult problems were presented when a body thus embalmed was submitted to chemical examination for poisons. The arsenic or mercury of the embalming fluid was of course always found in the remains, and it became a question as to whether a portion of that detected might not have been administered before death and had been the cause of the fatal issue. At the present time, however, owing to the prohibitory laws in many of the states and to the advantages obtained by using formaldehyd in the embalming process, arsenical and mercurial compounds are infrequently used. They have not, however, entirely disappeared from embalming fluids, especially in the states where their use is still permitted; and even in states where they are forbidden they are sometimes found in formaldehyd embalming fluids, usually, but not invariably, in small proportion, being introduced probably through negligence or accident. We are not justified in assuming that because an embalming fluid is made chiefly of formaldehyd it may not contain traces or more of arsenic or other poisons. Webster and Haines have recently investigated a case illustrating this fact.

While strychnin has but feeble antiseptic powers and therefore has no legitimate place in embalming fluids, yet on one occasion the author found a small amount of this alkaloid in an embalming fluid used on the body of a woman in whose remains strychnin was discovered upon chemical analysis. In this case the man accused by the state of having murdered the woman by strychnin was acquitted by reason of the presence of that poison in the embalming fluid.

If an embalming fluid containing formaldehyd is used, it should be remembered that this substance may seriously interfere with the detection of cyanids and certain other poisons, as has already been stated in this article (see page 37).

Statistics.—As a matter of both general and special interest we append tables, compiled from official information, giving the number and kind of fatal poisonings occurring in New York City and Chicago for the three years, 1918, 1919, and 1920.

POISONINGS IN NEW YORK CITY AND CHICAGO FOR YEARS 1918,
1919, AND 1920
NEW YORK CITY

	1918.	1919.	1920.
Accidental.....	673	600	573
Suicide.....	367	325	348
Homicide.....	11	10	9

¹ Mai, *Ztschr. f. anal. Chem.*, 1904, 93, 617.

² Compare the article on Postmortem Imbibition of Poisons, p. 874.

Name of Poison.	Accidental, 1918, 1919, 1920.			Suicide, 1918, 1919, 1920.			Homicide, 1918, 1919, 1920.		
Acetanilid.....	1	1							
Alcohol (ethyl).....				1					
Alcohol (methyl).....	9			1					
Alcohol (wood).....		54	19		2				
Aloin, belladonna, and strychnin.....		1							
Ammonia.....	2	2	1				1		
Arsenic (rat poison).....	1	3	1	1	2		3		
Atropin.....			1						
Benzene.....		1							
Benzol.....	1								
Bichlorid of mercury.....	6	2	7	9	13	14			
Botulism.....		1	9						
Bromid.....		1							
Camphorated oil.....				1					
Carbolic acid (phenol).....	6	6	3	15	15	17			
Carbon dioxid.....	2	1							
Carbon monoxid.....	1	1	2						
Castor oil seed.....	1								
Chloral.....		2							
Chloroform.....	2		1	1	1	3			
Coal gas.....	16	6	8						
Cocain.....	4	1	1						
Codein.....			1						
Creolin.....				1					
Caustic potash.....	1								
Cyanid (fumigation).....	2	13	8						
Ether.....	1								
Formaldehyd (fumigation).....			1						
Fumes of burning gun cotton.....	1								
Fumes of gasoline.....		1							
Heroin.....	7	15	5						
Hydrochloric acid.....	1		1			1			
Illuminating gas.....	528	435	428	311	285	288	9	6	8
Inhalation of mercurial fumes.....			1						
Iodin.....		1		2		2			
Kerosene.....		1							
Lead (occupational).....	1	2							
Lye.....			4	1					
Morphin.....	40	34	33	2	1	1			
Nitrobenzol.....	1		2						
Oil of wintergreen.....		1							
Opium.....	14	6	4						
Oxalic acid.....		1	3	1		1			
Paraldehyd.....			3						
Paris green.....				2					
Phosphorus.....	1			1	1	1			
Potassium cyanid.....				9	3	10			
Prussic acid.....				2					
Ptomain.....	6								
Quinin sulphate.....		1							
Ricin.....		1							
Salvarsan.....	5	2	11						
Sodium fluorid.....	1		2						
Somnos.....	1								
Strychnin.....	5	3	3	3		3			
Sulphuric acid.....				1		1			
Trinitrotoluene.....	2								
Veronal.....	3		8	1	2	2			
Undetermined.....			2	1			2	4	1
Total.....	673	600	573	367	325	348	11	10	9

CHICAGO

	1918.	1919.	1920.
Accidental.....	317	345	315
Industrial.....	...	3	...
Suicide.....	223	258	175
Homicide.....	21	11	11

Name of Poison.	Accidental, 1918, 1919, 1920.			Suicide, 1918, 1919, 1920.			Homicide, 1918, 1919, 1920.		
Acetanilid.....	...	...	2	...	...	...	...	...	...
Arsenic.....	1	2	1	2	1	1	...	...	...
Bichlorid of mercury.....	8	5	4	9	10	6	...	...	...
Bromidia.....	...	...	1	...	...	...	...	...	...
Calomel.....	1	...	1	...	...	...	...	...	...
Camphor, alcohol, ether, and oil.....	...	...	1	...	...	...	...	...	...
Chloral hydrate.....	...	3	2	1	...	...	...	...	...
Chloroform.....	1	2	...	3	1	5	...	...	...
Cocain.....	1	...	...	...	...	...	...	...	...
Corrosive.....	...	1	...	...	3	...	...	...	...
Cresolin.....	...	1	...	1	...	...	...	...	...
Emetin.....	1	...	...	...	...	...	...	...	...
Eucalyptus.....	1	...	...	...	...	...	...	...	...
Grain alcohol:	...	...	...	...	...	...	...	...	...
Home brew.....	...	...	3	...	...	...	...	...	...
Denatured with formaldehyd.....	...	...	1	...	...	...	...	...	...
Denatured with nitrobenzol.....	...	...	2	...	...	...	...	...	...
Heroin.....	1	...	...	...	...	...	...	...	...
Hoffman's drops.....	...	1	1	...	...	...	...	...	...
Hydrochloric acid.....	1	...	...	2	1	3	...	...	...
Illuminating gas.....	272	281	240	168	207	127	17	11	3
Iodin.....	...	...	1	1	...	...	...	...	...
Isobutyl alcohol.....	...	...	...	...	...	1	...	...	...
Kerosene.....	...	1	...	...	...	...	...	...	...
Lead (industrial 3).....	...	4	1	...	...	...	...	...	...
Liniment.....	1	...	...	1	...	...	...	...	...
Lye and ammonia-water.....	...	...	1	...	...	1	...	...	...
Lysol.....	5	2	4	1	3	3	1	...	...
Mercury.....	...	...	...	...	...	1	...	...	...
Morphin.....	3	6	...	2	1	...	...	...	...
Narcotic.....	...	...	...	2	...	...	...	...	...
Neosalvarsan.....	2	1	...	...	...	...	...	...	...
Nicotin.....	3	3	1	...	1	1	...	...	...
Nitric acid.....	...	...	1	...	...	2	...	...	...
Nitrobenzol.....	...	...	2	...	...	...	...	...	...
Opium, tincture of.....	...	...	...	...	1	...	...	...	...
Oxalic acid.....	...	...	...	...	1	1	...	...	...
Paraldehyd.....	...	...	1	...	...	...	...	...	...
Paregoric.....	1	...	...	...	...	...	...	...	...
Paris green.....	...	...	...	6	...	1	...	...	...
Phenol (carbolic acid).....	...	5	1	11	16	14	...	...	...
Phosphorus.....	...	1	...	...	...	...	...	...	...
Potassium cyanid.....	...	...	...	...	...	2	...	...	...
Ptomain.....	4	5	1	...	...	...	...	...	...
Rat poison.....	1	...	...	...	...	1	...	...	...
Sodium cyanid.....	1	3	...	6	9	2	3	...	...
Sodium hydroxid.....	...	1	...	...	...	...	...	...	...
Strychnin.....	5	5	3	6	2	...	...	...	...
Sulphuric acid.....	...	...	...	...	1	1	...	...	...
Veronal.....	2	1	2	...	...	1	...	...	...
Wood alcohol.....	...	13	23	...	...	...	...	...	8
Zinc stearate.....	...	...	1	...	...	...	...	...	...
Undetermined.....	1	1	13	1	...	1	...	...	...
Total.....	317	348	315	223	258	175	21	11	11

FORENSIC QUESTIONS RELATIVE TO POISONING

BY WALTER S. HAINES, M. D., AND RALPH W. WEBSTER, M. D.

CHICAGO, ILL.

As will be noted from the tables given at the end of the last section there are four general classes of poisoning which may assume forensic importance. In the order of frequency of occurrence these may be grouped as industrial, accidental, suicidal, and homicidal, although the industrial cases rarely appear in statistical tables of coroners' reports owing to the relative infrequency of death in the occupational types of poisoning. While the discussion given below has especial reference to criminal cases of poisoning, yet the questions presented may arise in any type of poisoning. It must be remembered that the industrial poisonings are usually chronic in type and do not, therefore, always present the same elements for analysis as do the more acute accidental, suicidal, or homicidal cases.

In practically every case of poisoning, which comes under investigation, certain questions of medicolegal importance arise. The expert must be prepared to meet these points as their solution is, usually, essential to the proper clearing up of the case. These questions will demand of the expert much acumen in solving them, and, if called to the witness stand, marked clearness of expression in explaining them, and especial firmness in maintaining his opinions when formed. We shall not attempt to foresee all possible questions which may be involved in any particular case, but shall limit our discussion to the more usual ones, which have been so well formulated by Tardieu¹ and, following him, by such authors as Kobert,² Witthaus,³ and others. Many of these questions have been discussed in different places in the text, but they are summarized here for convenience of reference.

I. Was the Death or Illness of the Subject Due to a Poison?—

This is an extremely important question and one which arises in every case of suspected poisoning under investigation. It dominates all other questions and compels the expert to establish if possible, beyond a doubt, the fact that a poisoning has or has not occurred. Before a definite answer may be given to the above question certain facts must be known to the expert. Disregarding the circumstantial evidence, which is of no moment to the expert, the demonstration of poisoning is definite when (1) the symptoms known to be caused by the poison

¹ *Étude Médico-Légale et Clinique sur l'Empoisonnement*, 2d ed., 1875, 113.

² *Lehrbuch der Intoxikationen*, 1902, i, 119.

³ *Medical Jurisprudence, Forensic Medicine, and Toxicology*, 1911, iv, 201.

have been noted during life; (2) the postmortem examination shows the presence of such lesions as the poison usually produces and the absence of other causes of death; and (3) the poisonous agent is shown to be present in the cadaver or in the vomit or excretions of the person poisoned.

1. The first indication of poisoning would probably be furnished by the nature of the symptoms shown by the victim; as a rule by their sudden appearance while he was in full health and, almost always, shortly after the ingestion of food or drink; by the violence and rapidity of these symptoms, and by their character, that is, by their primary localization and later generalization, followed frequently by a fatal termination.¹ In most industrial² and other chronic poisonings these remarks do not usually apply. It is true that, in some cases, the history of the symptoms shown by the subject is uncertain or obscure, owing to the lack of observation of them or to misinterpretation of them by the persons present with the victim. In other cases no symptoms may have been noted, as no one was present with the subject and, hence, no history could be obtained as to just what occurred after the ingestion of the suspected poison, except such information as may be given by the patient himself, which information is often unreliable. In such cases collateral evidence may be sufficient to warrant a conviction, even though one of the cardinal points of the proof of poisoning be missing. It is doubtful whether, in most cases, an expert should be asked to express an opinion as to the cause of the sickness or death if the symptoms are unknown.

If the victim does not die it would be extremely hazardous to give a positive opinion based alone on the symptoms noted, since, with but few exceptions, these are often practically identical with those produced by disease. However, in such cases, there often remains the possibility of detecting the suspected poison in the dejections and evacuations, such as the vomitus, stools, and urine.

2. When death follows a suspected poisoning the autopsy furnishes a second point of evidence as to the cause of death. Pathologic anatomy holds an important place in the medicolegal determination of poisoning. While inflammations of all degrees, interstitial hemorrhage, and fatty degeneration are the most commonly noted organic alterations produced by poisons, yet certain poisons produce results which, while not absolutely characteristic, are, however, extremely significant. It is hardly necessary to remark that care must be used not to confound the lesions of natural diseases or those produced by putrefaction with those of poisoning. Further, even when other causes of death than poisoning exist, these do not necessarily negative the possibility of poisoning. If poison be found in the body and signs of natural death also exist, it remains a question to be determined as to which of the two causes was operative. It is well established that the existence of one possible cause of death cannot be assumed to be exclusive proof that no other cause

¹ Compare section on General Principles of Toxicology, p. 26.

² See Chapter on Industrial Toxicology.

of death could have existed.¹ Postmortem findings are rarely conclusive since disease may produce the same appearances; but the lesions should be compatible with those produced by the suspected poison. However, it should be noted that occasionally characteristic appearances may be lacking. Both of the writers have investigated known cases of arsenical poisoning, for instance, in which no changes were found in the gastrointestinal tract.

3. Finally, the last determining element of poisoning is the finding of a substance in the body of the victim capable of causing the death. It is important to remember in this connection that the presence of the incriminating substance may be explained by some other cause than that of poisoning (see Question VII). Further, it should be noted that while the chemist may always extract from the body of a person who has died from poisoning the substance which exists in his organs, yet he is not always in a position to purify this substance and identify it. In some cases biologic tests may show that a toxic substance has been obtained, which is probably the cause of death, and such tests may demonstrate the fact that a poisoning has occurred even though the identity of the poison has not been established. Moreover, it should be borne in mind that a poison may be administered and yet none detected.² (See Question VI.)

II. What Poison Produced the Illness or Death?—This question assumes importance in every case of poisoning, especially of the criminal type. Indictments are usually drawn up in such a way as to cover the death of an individual from a definite known cause and, hence, the exact poison responsible for the death is usually stated. As mentioned above, the detection of a poison responsible for the symptoms and pathologic changes noted is one of the cardinal proofs of poisoning. Although the toxicologist may, in his investigations, cover the entire field of poisons, yet his chief attempts are directed toward the isolation of a poison which may cause the symptoms and changes observed. It is necessary that his finding be compatible with the symptoms and pathologic changes in order to establish the proof of poisoning. In some cases reported in the literature a certain poison has been known to have been administered, and yet the toxicologist has been unable to detect the presence of such poison in the organs of the victim.³ Here, other evidence than that of the finding of the poison must assume great importance in order to insure a conviction. In other words, the finding of a poison in the body is not absolutely necessary to the establishment of the fact that a poisoning has occurred.⁴

It is to be remembered that it is not usually possible for the toxicologist to isolate the poison in the form in which it is administered. Thus, in the case of poisoning from arsenic trioxid, this compound is

¹ Compare section on General Principles of Toxicology, p. 37.

² See sections on General Principles of Toxicology, p. 39, and Alkaloidal Poisons, p. 546.

³ Compare General Principles of Toxicology, p. 40, and Alkaloidal Poisons, p. 546.

⁴ See Palmer case, General Principles of Toxicology, p. 39.

not generally obtained in the examinations, except in those cases in which it may be found adhering to the mucous membrane of the stomach or intestines. Arsenical poisoning is shown in the investigation by the presence of an arsenical mirror as in the Marsh test, or by the coating of copper as in the Reinsch test, or by the precipitation of the sulphid of arsenic or of the magnesium pyro-arsenate, or by other analogous tests. The same may be said of the alkaloids as a group. One rarely obtains these compounds in a state of absolute purity, but his tests of identification are certain and definite. Courts may demand the production of the substance isolated, and hence it is wise for the toxicologist to save some of his material to offer in evidence if called upon to do so.

III. Was the Substance Employed Capable of Producing Death?—This question raises the point upon which the definition of a poison is based. Nothing would be more simple to answer if this property of causing death or of injuring health was an essential and inherent characteristic of the substance itself. One cannot deny that in many cases the form in which the substance is prepared, combined, and administered determines whether it is capable of causing death or injury. The intent to kill may be present, and yet the form in which the substance is administered prevents its fatal action. The answer to this question must take cognizance of the various factors which influence the action of drugs and poisons. Each case must be determined on the circumstances surrounding it and the clinical history connected with it.¹

IV. Was the Poison Taken in Sufficient Quantity to Produce Death?—This question cannot always be answered positively, although an opinion may be usually ventured. It is evident that there are two factors which must be considered: (1) What is the lethal dose of the poison itself? and (2) how much of the poison was actually taken in the case under investigation?

1. Concerning the lethal dose of the various poisons it is to be said that the amount of a poison necessary to produce death has been determined, within certain limits, by observation of known cases of poisoning and by animal experimentation. While this latter method of arriving at the lethal dose of a poison in man from a consideration of the dosage necessary to produce death in animals is faulty, yet it is of some general value and must be regarded. If, then, in his examinations the toxicologist discovers an amount of a poison, which is beyond the limits of the lethal dose of this poison, it is clear that he is justified in stating that the quantity found was sufficient to account for the death. On the other hand, while his findings may be such as indicate a non-lethal dose, still, the amount detected may be far in excess of the amount which would be legitimately present from ordinary medication or accidental impurities. Under these latter circumstances suspicion would at least attach to the possibility of poisoning.²

¹ See section on General Principles of Toxicology, p. 21.

² See Lethal Dose, under the various toxicologic subjects discussed.

In trials of criminal cases the expert is not infrequently asked as to whether he found sufficient poison in the stomach to produce death. In this connection it is to be remembered that the amount of poison found in the stomach is ordinarily of but little consequence in deciding as to the production of death by a poison, as the poison in the stomach has not as yet been absorbed and, in consequence, has had nothing whatever to do with the production of death, except in cases of corrosive poisoning. A very large amount of poison might be found in the stomach and little or none in the organs, such as the liver, kidneys, and brain. In such cases one would be justified in stating that he had found a fatal amount in the stomach only if it had been absorbed. Hence, in his examinations the toxicologist must find a lethal amount outside of the stomach and intestines, or else refrain from stating that he has found a lethal quantity unless the relations of that discovered in the stomach are clearly explained. While it is true that some poisons, such as arsenic and morphin, are re-excreted into the stomach after absorption, yet this fact does not militate against the above statements, as the amounts so excreted would not be such as to influence the answer to the above question to any extent.¹

2. As regards the amount of poison actually taken by the victim in any case of poisoning it is a more than difficult matter to state. In the first place the amount of a poison isolated represents only that obtained from a few organs. The entire body is practically never examined. The amount isolated may represent a fatal quantity or it may be infinitesimal. With inorganic poisons the yield is usually actually quantitative for the organs examined, but with organic poisons there is always more or less loss, the amount obtained representing an undetermined fraction of the total amount present.² Secondly, the amount isolated represents only that which remains in the body, the amount lost by vomiting, purging, and elimination through other channels not being determined. For these reasons the expert is in a position to state only that such an amount was isolated in his examinations and that the amount taken was more than he obtained. If the amount so obtained was a lethal quantity he may state so, but if he did not isolate a fatal quantity he might, nevertheless, be in a position to state that a lethal amount had been given, basing his conclusions upon known facts of distribution and elimination. While it is not an absolute essential in the establishment of death from poison that a lethal dose be recovered by the toxicologist from the cadaver, yet the examinations should be extensive enough, if possible, to permit the isolation of such a fatal amount, as this considerably strengthens the case. When the quantity of poison is small the clinical history must be taken into consideration, the frequency and amount of vomiting, the purging, and the time elapsing before death being important factors in solving the question of possible elimination.

¹ Compare section on General Principles of Toxicology, p. 39.

² See General Principles of Toxicology, p. 61, and Alkaloidal Poisons, p. 433.

V. When and How was the Poison Taken?—It is usually of great importance in most criminal cases to establish with certainty the exact time of commission of the crime. Poisoning is no exception to this rule, although it is a difficult matter to fix the precise time of administration, owing to the secrecy with which poison is usually given. The mode of onset, the rapidity of the symptoms, and the continuance or remission of these symptoms furnish evidence as to the possible time of administration and whether or not there were successive stages in the poisoning. While most poisons act rapidly, some much more so than others, yet there are occasional cases reported in which the symptoms did not appear for several hours after taking the poison.¹ These cases are the marked exception, so that the time of administration may generally be set down as within an hour of the appearance of the first symptoms, if this time be known. Of course, much will depend upon the various conditions which favor or retard the absorption of a drug.

As to the method of administration of the poison one can state that most criminal poisonings are by mouth. Naturally, the symptoms appear much quicker when the poison is inhaled or given hypodermically or intravenously than when given by mouth, so that this must be taken into consideration in forming a conclusion. While some poisons, such as arsenic and morphin, are excreted into the stomach when administered by channels other than the mouth, yet, in a general way, the finding of more than traces of the poison in the stomach would point to its administration by the mouth. On the other hand, failure to find it in the stomach would not mean that it had not been given by mouth, as absorption may have been complete or there may have been total loss by vomiting.

VI. May a Poisoning Have Occurred and the Poison Either Be or Have Become Undetectable?—There are a certain number of poisons which are not determinable by chemical means at present known or are converted in the body after death into substances which are normally present; other poisons are not capable of detection by physiologic tests, either because they show no characteristic symptoms or because the symptoms have been insufficiently studied; while there are but few which are shown conclusively by pathologic examination. For these reasons a poison may be administered and may escape detection by any or all of the methods available.² Poisons may be removed from the stomach and intestines by repeated vomiting, purging, and absorption, so that none will be found in these organs on examination. Further, if life continues sufficiently long, all of the absorbed poison may be eliminated from the body. Moreover, organic bodies, especially the alkaloids and glucosids, are more or less rapidly changed by putrefactive processes to other substances which do not possess characteristic reactions sufficient for their detection. The time after death with which alkaloids, for instance, may be detected in the

¹ See section on General Principles of Toxicology, p. 26.

² See sections on General Principles of Toxicology, p. 37, and Alkaloidal Poisons, p. 546.

body varies with different alkaloids, so that no definite statement may be made as to this.¹ Volatile poisons, such as hydrocyanic acid, may disappear quickly and thus escape detection.

It is evident, therefore, that a notable amount of a poison may be administered and yet escape detection in the body after death. It is true that the possibility of detecting the inorganic poisons is greater than is the case with the organic, after the lapse of considerable time, but it must be remembered that all of either the inorganic or organic poison may have been eliminated from the body before the examination is made.

VII. May the Poison Extracted from the Cadaver Have an Origin Other Than in Poisoning?—It should be stated that the finding of a toxic substance in the organs does not of itself prove a poisoning. Further, all of the symptoms and pathologic findings associated with the administration of this poison may be present and yet a criminal poisoning not be present. It must be admitted that certain of our medicinal preparations sometimes contain impurities, which may, under certain conditions, be found in the examinations of the organs of a supposed victim of poisoning.

There are cases of mistake in filling prescriptions in which poisons have been substituted for harmless drugs. These facts must be given due weight and the above question answered by an affirmative. If the amount of poison be small, the question will always arise as to the possibility of the medicinal origin of the poison found. After the administration of as little as $\frac{1}{60}$ grain of strychnin three times a day for two or three days, strychnin may be unequivocally shown in the liver and brain.² Similarly, mercury may be detected in the bodies of those who have taken compound cathartic pills or other mercurial preparations; while the finding of arsenic may be traceable to the administration of salvarsan or other antisyphilitic remedy.

Moreover, food products occasionally contain small amounts of poisonous impurities, especially of the inorganic type, so that one may find in his examinations traces of such substances, even in cases of undoubted poisoning by other substances. Thus, barium salts are found, as an impurity, in such common articles of diet as vinegar and common salt, so that the detection of barium in toxicologic examinations might be very confusing and difficult to interpret were not the possibilities of extraneous origin considered.³

Not a small number of persons are addicted to the use of various drugs, so that one would expect to find, as he actually does, such drugs in the organs of these habitués. This fact must be borne in mind in every toxicologic examination.

A further possibility of an extraneous origin of a poison is the artificial introduction of the poison into the body after death, either by imbibition⁴ from the soil or surrounding contaminated objects or by

¹ See section on Alkaloidal Poisons, p. 436.

² Ibid., p. 587.

³ See section on Inorganic Poisons, p. 284.

⁴ See section on Postmortem Imbibition of Poisons, p. 861.

intentional placing of poison into the stomach in order to cast doubt upon the actual cause of death. Such procedures as the latter are noted, not infrequently in the literature, generally, we believe, without sufficient proof of such action.

In this connection one must not lose sight of the fact that poison may be introduced into the body after death by the use of embalming fluids, containing arsenic or formaldehyd, for instance. About one-half of our states prohibit the use of arsenic in such fluids, but the others allow it. Even in states in which arsenical embalming fluids are not allowed, it is not always possible to state that no arsenic is present without a thorough examination of the fluid for arsenic. While such fluids may not be in the strict sense of the word "arsenical," yet they may contain even appreciable amounts of arsenic as an impurity or there may have been some of an arsenical embalming fluid mixed with a non-arsenical fluid by mistake, as many companies prepare both the arsenical and non-arsenical types of embalming fluids. The detection of arsenic in the body can have no value if an arsenical fluid has been employed in embalming, so that a very careful examination of the actual fluid used in the embalming of the body under investigation must be made before a definite opinion as to the source of the arsenic can be maintained. Further, while formaldehyd embalming fluids rarely contain anything that would give rise to suspicion of poisoning, yet their use will make the detection of wood alcohol poisoning a difficult process and may destroy all possibility of detecting cyanids in the organs.¹ Moreover, extraneous material has at times been added to formaldehyd embalming fluids by parties interested in the case under investigation in order to cast doubt upon the findings of the chemist. Such an experience in finding strychnin in a formaldehyd embalming fluid has occurred twice in the experience of one of us (Haines).

So, also, the question must arise, in any toxicologic investigation, as to the possibility of introduction of poisons in the process of the examinations of the chemist. It is needless to state that such an error could arise only in cases of sheer negligence in testing the reagents used in making the tests. If the chemist does not know the purity of his reagents, his results may be very faulty indeed.

VIII. Was the Poisoning Suicidal, Accidental, or Homicidal?

—The answer to this question is one which does not usually devolve upon the medicolegal expert. The circumstantial evidence in the case is generally such as to point to the possibilities. However, the expert may give evidence as to the character, the color, the taste, etc. of the poison and in this way aid in the possible solution of the question. The method of administration, if this be known, of the drug and the finding of the poison in household remedies which were used by the victim may tend to throw some light on the case.

IX.—May the Poisoning be Simulated?—In answering this question it is to be said that the symptoms may be simulated, but the pathologic and chemical findings cannot. There are, undoubtedly, a

¹ See section on Non-alkaloid Organic Poisons, p. 685.

large number of persons who believe that they are being poisoned and who fancy that everything they eat or drink is poisoned. So settled may this delusion become that symptoms of a definite poisoning may be simulated by them, this being a not infrequent occurrence with hysteric patients.

In this connection it may be noted that there are authentic cases where real poisoning has occurred in which the poison given produced much the same symptomatology as a natural disease, which may have been epidemic at the time. Thus, Kobert¹ cites a case of poisoning with tartar emetic during an epidemic of cholera, the poisoner thinking that the death would be attributed to the disease. Cases are on record in which persons have believed that they were being poisoned and have introduced poisons into their own food in order to throw suspicion upon some innocent person.

¹ Lehrbuch der Intoxikationen, 1902, i, 122.

THE TECHNIC OF MEDICOLEGAL POST-MORTEM EXAMINATION

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INTRODUCTION

A POSTMORTEM examination for medicolegal purposes is generally made in order to determine, as far as possible in the power of medical science, the cause and the kind of death. In order that all the information bearing upon this problem which can be gathered from the examination of a dead body may be obtained, it is essential that the examination be made in a thorough and exhaustive manner, by competent persons; and that the results of the observations be made more or less permanent by being recorded properly. It is not sufficient simply to demonstrate the existence of a fatal lesion, because all other possibly fatal lesions of the organs of a body must be shown, by actual examination, to be absent before any existing lesion can be regarded as the sole cause of death. If various lesions co-exist, the possible interdependence of these lesions and the relations of each to the causation of death must be determined and made clear to the administrators of the law. Hence, a postmortem examination for legal purposes must, if the conclusions based upon its results are to stand the test of scientific and judicial scrutiny, include a trustworthy investigation of practically all the organs and structures of the body.

Accurate observations, completeness, and correct conclusions are obtainable only when the postmortem examination is made according to a definite or systematic plan, by means of which regions and organs are successively examined without disturbing the relations and appearances of those being or yet to be examined. In order to obtain the improved results thus attainable, many governments prescribe by rules and regulations the exact order and steps to be followed in medicolegal examinations. When such matters are left in the hands of the individual physician, it is believed that the following directions will afford material aid in reaching the desired result.

INSTRUMENTS AND UTENSILS

The following instruments and appliances are essential for proper medicolegal postmortem examinations.

Knives.—The long incisions and the coarse dissection are made with a so-called section knife. This knife should possess a deep bellied

blade about 2 cm. (0.79 in.) broad and 11 cm. (4.33 in.) long, with a heavy, preferably wooden, handle about 2 cm. (0.79 in.) thick and 12 or 13 cm. (4.72 to 5.11 in.) long, and modeled so that it can be firmly grasped with the whole hand.

The more minute dissection requires ordinary scalpels.

The brain knife is a very useful and important instrument employed for incising the organs so that smooth and extensive surfaces are made, upon which the structural conditions may be studied. The most universally convenient form of the brain knife is like an amputation knife; it should have a total length of about 30 cm. (12 in.), equally divided between the blade and the handle; the blade should be about 1.8 cm. (0.7 in.) broad, and so strong that it does not bend or feather too easily. The thin, double-edged brain knife with the rounded end is more especially serviceable in incising the brain.

The myelotome (Pick) is a small knife used in removing the brain by dividing the medulla from the spinal cord in such a manner as to secure exactly transverse, and not oblique, cut surfaces. It consists of a blade 1.5 cm. (0.59 in.) long and 4 mm. (0.16 in.) broad, and rounded at the extremity. This blade is attached to a stem at an angle of about 100 degrees, the stem, with its wooden handle, being about 24 cm. (9.5 in.) long.

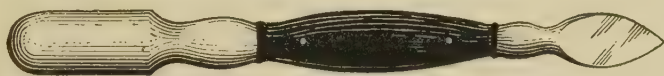


FIG. 12.—Raspatory for removing the periosteum, 18 cm. long.

Scissors.—Anatomic scissors with one blunt and one sharp blade are necessary. Probe-pointed scissors are very useful for incising vessels and canals of various kinds. The enterotome, or intestinal scissors, has one of the blades provided with a blunt, projecting extremity which should be perfectly smooth and free from sharp points or edges that might catch in the folds of the mucous membrane of the intestines or the columnæ carneæ of the heart. A convenient size has blades about 9 cm. (3.5 in.) long, and the blunt projection is about 8 mm. (0.31 in.) long, 6 mm. (0.24 in.) broad, and 4 mm. (0.16 in.) thick. In use, the blade with the blunt projection is always lowermost. Stronger bone scissors are useful for cutting the laryngeal cartilages, the ribs, etc.

Dissecting Forceps.—Two pairs, one strong and large, one small and delicate, are required; “rat-tooth” forceps are useful.

Probes, large and small, of metal or bone and a catheter are necessary. A raspatory for removing the periosteum, especially in the examination of fractures, is needed. (See Fig. 12.)

Saws.—A butcher’s saw will answer the purpose very well. A bone-saw with a movable back and detachable blade, with not too fine teeth and well set, is preferable. For the purpose of removing parts from the base of the skull a keyhole saw may be desirable, and in order to divide long bones in a longitudinal direction a band saw is almost necessary.

For sawing the laminae of the spinal column a saw with a curved handle and rounded broad blade, 10 cm. (4 in.) broad at the broadest part and 30 cm. (12 in.) long (see Fig. 13) is very useful. The double saw with removable blades, known as Luer's rachiotome, is now quite generally used (see Fig. 14).

Chisels.—A chisel with a straight edge and a strong wooden handle, the blade being about 3 cm. (1.18 in.) broad, will answer. A T-shaped steel chisel with a blade about 6 cm. (2.36 in.) long, 1.8 cm. (0.7 in.)

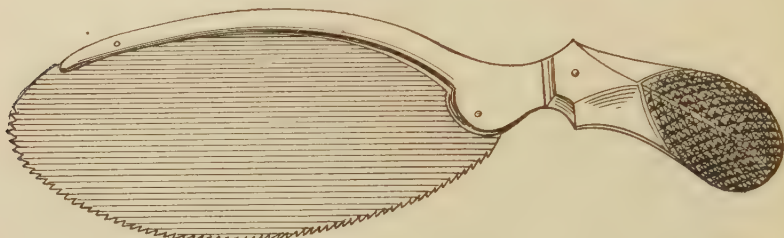


FIG. 13.—Single-bladed saw, with rounded blade, 30 cm. (12 in.) long and 10 cm. (4 in.) broad at the broadest part, for removing vertebral arches.

broad, and 6 mm. (0.24 in.) thick, attached at right angles to the center of a steel handle 9 cm. (3.5 in.) long and about 1 cm. (0.39 in.) thick, is used to loosen the calvaria from the pachymeninx. A heavy wooden or rawhide mallet or an ordinary steel hammer is also required.

Linear and Liquid Measures.—A brass or wooden foot-rule, graduated into inches and centimeters, is necessary; also a steel or cloth tape-measure. One measure in centimeters, about 30 cm. long and flexible, will be found of great service. Caliper compasses, with graduated cross-bar, are handy. Graduated cups or glasses for measur-

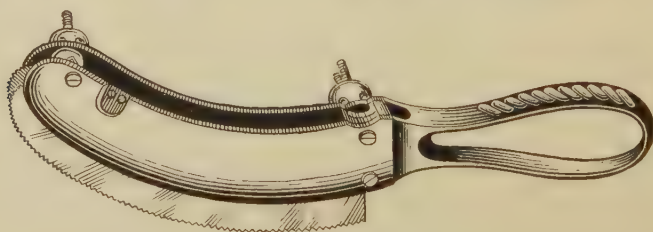


FIG. 14.—Double-bladed saw for removal of the spinal cord (Luer's rachiotome).

ing the quantity of liquids and for volumetric measurement of solid bodies by replacement of water are necessary. Every set of postmortem instruments should include some kind of measure of known and exact capacity.

Scales.—Weighing determines actual increase or decrease on part of an organ more accurately than measurement. In large dead-houses scales should be arranged for the weighing of the whole cadaver; a fulcrum and lever arrangement underneath the postmortem table would weigh the body as it is placed in position for the autopsy. Scales capable

of weighing up to 3000 or 4000 gm. (8 to 10 lbs.), with suitably subdivided weights, are necessary in order to weigh the organs. When the examination is made in a private house it may be difficult or out of the question to secure the weights of the organs of the body.

Among other instruments necessary may be mentioned postmortem needles and thread (Barbour's linen thread, No. 25, is sufficiently strong). Sponges, pails, vessels, plates, and bottles are articles found in all post-mortem rooms; when the examination is made in a private house it is well to come provided with the necessary sponges and bottles.

Histologic, Chemical, and Bacteriologic Utensils.—At the present time the satisfactory examination of the dead body very frequently requires microscopic, bacteriologic, and chemical investigation of the tissues and fluids, and in many cases the autopsy is in reality only the first step in the study of the case. Inasmuch as the ultimate result depends upon the work being complete and correct from the beginning, it may be necessary for the examiner in private cases, in the country or removed from the conveniences of a fully-equipped post-mortem room, to bring with him suitable fixing solutions for histologic purposes, glass-stoppered jars for receipt of the organs in cases of poisoning, suspected or otherwise, and utensils for securing, during the course of the autopsy, proper material for subsequent bacteriologic examination.

For detailed information concerning the solutions necessary to preserve material for histologic study, and for directions how to secure material for bacteriologic purposes, reference is made to the works on histologic and bacteriologic technic. For this last purpose the so-called Pasteur pipets, made by drawing out glass tubing at one end to a fine point, which is closed by fusing the glass there, cottoned at the other end, and sterilized with dry heat, are most serviceable. They may be sterilized in a cylindrical metal case which opens at one end and contains from thirty to fifty pipets easily transported in the case.

THE RECORD

It is essential that the observations made during a postmortem examination be carefully recorded at the time, and in such a manner that the notes can be used for reference on the witness stand. In this record should be described, as completely, accurately, and objectively as possible, that which is actually observed; the description should be concise, clear, and unembellished, and should not include deductions or opinions except under the head of conclusions or diagnosis. If the record is dictated during the course of the examination it should be verified carefully by the examiner when it is finished.

The record should be made in the same order as the examination, and for this reason each step in the autopsy should be completed, if possible, before the next is commenced. The record consequently embodies the following subdivisions:

1. Preliminary data, including name, sex, age, color, time and place, of death and examination, the names of the persons present, and,

invariably, of those by whom the body is identified. If positive identification by some one who knew the dead person during life is not obtainable, a detailed description of the characteristics of the body must be taken down under the heading of inspection.

2. Summary of the Clinical History.—Clinical information should be obtained, when possible, from the medical attendant, the friends, the police, or the hospital records, so that the postmortem examination may be made as intelligently as this knowledge makes it practicable.

3. Inspection.—Under this heading are included complete notes as to the size, the development, the nutrition, the rigor mortis, the livores mortis, and the evidences of decomposition that may be present. All marks of violence must be carefully described, with detailed minuteness as to location with reference to fixed anatomic landmarks, size, shape, color, etc. If the body is that of an unknown person, the necessary descriptive details must be ascertained and carefully recorded.

4. Charts.—For many purposes external injuries, such as bullet or other wounds, broken bones, marks of identification, such as tattooing, amputated fingers, etc., charts will be found useful. Quite complete charts for the exterior of the body, the bony skeleton, and the brain may be procured from various medical publishing houses. The charts, with the lesions and injuries so indicated, should form part of the record.

5. Internal Examination.—The record should contain a detailed objective account of the appearances observed in the cavities and organs of the body. The size and weight of the organs, the size of abnormal areas and growths, should be inserted in actual figures as often as possible, rather than in relative measurements.

6. Diagnosis or Conclusions.—Here are enumerated, in the most natural order, the various anatomic changes observed. In case the record is sent as a whole to some court or corporation, the summary should contain, in clear and concise terms, the conclusions as regards the cause and manner of death, formed by the physician from the examination recorded.

In the variety of medicolegal cases known as coroner's cases, the statement wanted from the physician who makes the autopsy is one that clearly and concisely describes the cause of death, because this is determined by a jury of laymen, and the report should be so worded that a fairly intelligent layman can readily grasp its import; but it need not always include the many and otherwise important details that are found in the complete record made for future reference—as, for instance, during a criminal trial.

EXAMINATION OF THE BODY

The general arrangements of the postmortem room of the modern hospital do not require any detailed description. Unobstructed daylight is essential for correct interpretation of colors, and a medicolegal exam-

ination, completed for especially urgent reasons by artificial light, may be open to criticism, and the observations should, under such circumstances, always be controlled by microscopic examination, more particularly when it concerns diffuse lesions of the parenchymatous organs.

In a private house the available room with the best light and the least furniture should be selected in which to hold the autopsy. The body may be placed on a kitchen table or left lying on the undertaker's stretcher; it is advisable to protect the floor around the body by means of oilcloths or old quilts. Abundant provisions, in the form of pails, basins, pitchers, and warm and cold water, must be made for cleanliness, towels and sponges should be at hand, and trays or plates on which to place the organs are also necessary.

The operator should take precautions to see that his work is done in as clean a manner as possible. An oblong cup of copper fastened to the postmortem table at the foot in the middle with plenty of room on each side for the feet and legs, with an overhead connection to provide running water, is of great value in preventing infections because of its accessibility.

The hands and the instruments should be washed frequently during the course of the examination; blood and inflammatory exudate dried on the fingers are unpleasant and dull the sensitiveness of the skin. The knives should be clean when the organs are incised.

In the hospital postmortem room water may be allowed to run over the body at frequent intervals, but its liberal use must not in any way obscure the condition of the body cavities or their contents. Water must not be allowed to come in contact with the spinal cord or the brain in case these structures are to be hardened in Müller's fluid.

The body to be examined is placed upon the table in the supine position, and all clothing, including the stockings, is removed. Under all circumstances the examination of the exterior of the body is invariably first in order.

INSPECTION

The external examination or inspection of a dead body determines not only the general physical characteristics of the body, but also the condition of the skin, the subcutaneous tissue, the mucous membranes, the accessible canals and cavities, as well as of the superficial organs, such as the eye, as regards morbid changes or wounds. In the case of unknown bodies the inspection aims to furnish such positive data concerning the physical appearance as may form the basis for a definite identification.

Inspection falls into two parts: a general, in which the general external conditions are studied; and a special, in which the particular external conditions of the individual parts of the body are examined.

General inspection determines the height, sex, approximate age, color and state of the skin in general, stature, state of general nutrition, and the degree and nature of the postmortem changes present. Whenever possible, the exact weight of the body should be determined.

The body length is measured by means of a tape or anthropologic measure placed upon the table by the side of the cadaver, or the edge of the table may be a graduated scale. The distance determined is that between the highest point of the head and the center of the sole of the heel.

The **color** is usually determined by a glance, but inveterate filth, coal-dust, etc., may make it difficult to establish the exact shade of the normal color of the skin; in such cases the surface must be cleansed well.

The skin, in general, may contain varying amounts of blood; its tension and elasticity may be tested by raising it into folds; diffuse eruptions, pigmentations, minute hemorrhages, and edema are noted.

The **stature** may be large and powerful, or smaller, finer, and delicate; evident disproportions between the various parts of the skeleton may exist.

The **state of the general nutrition** is shown by the fulness and roundness of the form and the quantity of subcutaneous adipose tissue.

The **degree of rigor mortis** present is determined; it is to be remembered that cadaveric rigidity first shows itself about the muscles of the lower jaw, from which it gradually extends downward; it disappears in the same sequence.

The **livores mortis**, or postmortem lividities, are of normal postmortem occurrence. They are reddish or livid discolorations appearing upon the undermost parts of the body that are not subjected to pressure, and are due to the simple gravitation of the intravascular blood. Diffusion of the blood coloring-matter into the perivascular tissue may occur when decomposition begins.

Decomposition shows itself first as greenish discolorations in those regions where the viscera are nearest the surface, as in the lateral and inguinal parts of the abdomen. Advanced decomposition produces extensive discolorations; the tissues become infiltrated with fluids and gases; by accurate observation of the extent of the changes, the circumstances, etc., an approximate idea may be formed as to the length of time that has elapsed since death.

In medicolegal autopsies the nature of all areas of discoloration upon the dead body must be definitely settled, and the following are some of the more important points to consider:

Their location, size, and shape; the effects of pressure in removing the color; the exact shades of color observed; the absence or presence of tension or elevation of the area; and, finally, the condition of the underlying tissue as regards infiltration with fluid or clotted blood. None of the usual and early postmortem discolorations is accompanied by swellings, but extravasations usually are. The postmortem hypostasis stain can be removed for a moment by pressure, and does not, on incision, show any free blood in the tissues outside of the vessels. Extravasations due to violence or other causes present areas in which the tissue, on incision, is found infiltrated with free fluid or clotted blood, due to the rupture of the blood-vessels. Extravasations produced immediately after death cannot, under some circumstances, be distin-

guished from antemortem infiltrations, and decomposition may so change appearances that a correct interpretation may become very difficult.

Inspection of the exterior of the individual parts of the body must be minute and systematic, and should take up the various regions in the following order:

The Head.—Peculiarities of formation are to be noted. The quantity, length, and color of the hair and the beard; the condition of the scalp as regards wounds and scars; the eyelids, eyeballs, and pupils; deepened hollows of the face, acute emaciation; the state of the nose, mouth, and ears as regards foreign bodies, blood, and other fluids; the color of the lips and the nose; burns or corrosions of the lips; the teeth, the tongue—these are some of the more important structures and points to be investigated.

The Neck.—The length and thickness of the neck are to be noticed, and it must be closely examined for livid spots and marks of violence, as well as for glandular enlargements, asymmetry, etc.

The Chest.—Here are to be noted in general the dimensions, possible asymmetries, and other deviations in form; in women, the fullness of the mammary glands and the absence or presence of milk in them must be studied; on the back of the chest bedsores, needle wounds (lumbar puncture), deviations from a straight line of the spinous processes, etc.

The Abdomen.—The degree of abdominal distention; the condition of the inguinal and crural regions with reference to hernia; the presence of lineæ albicantiæ, of scars, and of swellings—these are some of the subjects for inspection.

The External Genitals and the Anus.—In women suspected of having died from the results of abortion the external genitals are to be carefully examined for ruptures and tears, punctures, and other wounds, for foreign bodies, inflammatory lesions, and peculiar discharges. In cases of assault, the condition of the hymen and the introitus vaginæ must be examined for evidences of violence; and the fluids present, as well as the stains upon the clothing, must be studied microscopically for spermatozoa. In men the glans penis and the prepuce are to be searched for syphilitic and other cicatrices. The anus should also be investigated for inflammatory and other changes, as well as for foreign bodies.

The Extremities.—Finally, the extremities are taken up and examined for defects, deformities, edema, ulcers, scars, gouty deposits, articular changes, external injuries, etc.

While the external examination very often consists in mere ocular and palpatory investigation, the examiner should never hesitate or delay to incise areas that attract his attention. Later on in the course of the autopsy the surface may become soiled, or the examination of such places may be neglected.

All wounds must be accurately described and located with reference to fixed anatomic landmarks. The dimensions of wounds should be accurately and precisely measured and stated in definite figures, and not in comparative or approximate terms. Penetrating wounds must

not be probed indiscriminately, because of the liability of rupturing the walls of important cavities and of complicating the extent of the original wound. Careful dissection should be made to determine the course and direction of the wounds; sometimes this can best be done after opening the cavities of the body, but as a general rule the external examination should be quite fully finished before the cavities are opened, because thereafter the turning of the body may be undesirable and the anatomic relations are often quickly disturbed.

INSPECTION IN THE CASE OF UNKNOWN, BURNED, AND DECOMPOSED BODIES

The physical and other peculiarities of dead unknown persons require the most careful examination and record for the purpose of aiding possible future identification. Whenever the state of the body is such as to warrant it, one or more good photographs should be taken of the face; in many cases different views are desirable. Under all circumstances, in addition to the photographs, careful observations in regard to the following conditions and facts are to be recorded—to wit: Age, sex, height, weight, build, forehead, face, eyes, nose, hair, teeth, beard, mustache, complexion, scars, marks, condition of fingers and toes, overcoat, coat, vest, pantaloons, underwear, shawl, cloak, dress, boots, shoes, stockings, necktie, personal property, probable occupation and reasons for determining it, etc., as well as a note of the locality where the body was found.

In the case of bodies changed beyond ready recognition by the destructive action of fire, the identification may be favored by such general information as can be obtained in regard to the sex, the height, etc., of the body; while certain conditions of the teeth, bits of clothing, finger-rings, certain peculiar deformities, etc., may determine the identity.

In the case of greatly decomposed bodies, an effort should first be made, when necessary, to determine the sex by finding perhaps distinct remains of the uterus, which is one of the last structures to undergo disintegration; the condition of the hair, skeletal peculiarities, etc., must not be forgotten.

All unknown, decomposed, and changed bodies should be examined in the general manner indicated, and physical peculiarities, such as peculiar teeth, hernia, malformations, deformities after fractures, etc., should always be looked for, as they play a prominent part in determining the identity.

INSPECTION OF THE SURROUNDINGS OF THE BODY

In medicolegal cases the external inspection often includes an examination of the clothing of the body for tears, holes, stains, etc.; and also of the premises where the body was found. Particular attention is to be given to the position of the body with reference to the furniture, blood-stains, vomited matter, glasses, powders, medicines, etc. Stains upon the carpet, bedclothes, or personal clothing may have to be examined. Instruments and other articles that are to be preserved

should be placed under lock and key for the time being. Photographs of the room or premises may be valuable.

FROZEN BODIES

In case the body be frozen arrangements must be made for thawing it out thoroughly before any internal examination is attempted, as many organs—the brain, for instance—cannot be removed, if frozen, without fatal damage; and also because the consistence of various tissues, the absence or presence of thrombosis, etc., cannot be made out in structures partly or completely frozen. According to the German regulations for guidance in conducting postmortem examinations for legal purposes, the use of warm water or other warm substances for expediting thawing is not allowed.

EMBALMED BODIES

In the case of embalmed bodies great care must be exercised in interpreting the appearances observed in the tissues, as the fluids employed are often capable of greatly changing the consistence and color of the structures with which they come in contact.

Arterial embalming precludes the formation of any correct idea as to the blood distribution in the organs; and in the lungs the parenchyma may present a rough, shriveled appearance, as though extensive coagulation had taken place.

In "cavity embalming" a long, coarse trocar is passed into the abdomen, and the intestines are punctured in as many places as possible, and then penetrations are made in the direction of the heart, great blood-vessels, and lungs; and, finally, large quantities of strong fluid are pumped into the cannula. One of us (Hektoen) is acquainted with instances in which punctures of the heart produced in this manner were mistaken for spontaneous ruptures. Occasionally a quantity of embalming fluid is forced into the mouth, and small portions may find their way down into the lungs and produce anomalous appearances, quite perplexing to the uninitiated. And it might not be altogether impossible for some of the fluid to gravitate into the stomach, to the annoyance and mystification of the toxicologist.

INTERNAL EXAMINATION

The Order of the Internal Examination.—In medicolegal cases it is the rule to direct attention first to that part or region of the body in which there are grounds to believe that the cause of death may be found, and then to examine the remaining cavities in whatever order may be most serviceable. All postmortem technic is based upon the general rule that regions and organs are to be successively examined without disturbing the relations and appearances of structures yet to be investigated; and whenever it becomes necessary, on account of special conditions, to modify the generally accepted order of procedure, then this general rule should likewise govern the modification.

Generally speaking, a complete medicolegal postmortem should begin

with the head, and then the spinal cord is best examined, especially in case the examination is made in a private house. Turning the body on the anterior surface after having opened the chest and abdomen is, under all circumstances, an uncleanly operation; but in the hospital postmortem room the specially constructed tables in the main remove this objection to leaving the spinal cord until the last if desired. Then follow the long anterior incision and the preliminary inspection of the cavities of the trunk, after which the organs of the neck, thorax, and abdomen are examined, in the order named. The order in which the single organs and structures in these cavities are examined is not of essential importance, but the underlying principle should be that organs functionally related and anatomically continuous are examined one after the other, and, if possible, without any separation of continuous structures, until it is shown that such separation does not obscure morbid conditions or mutilate instructive specimens. For these reasons the following technical description directs the removal and examination of each of the respiratory, digestive, and genito-urinary tracts as far as possible in one continuous whole.

In medicolegal cases it is best to avoid the cutting across of large vessels near the heart until the relative amount of blood in the heart cavities has been determined; and, consequently, it is recommended to make an early preliminary examination of the heart for this purpose, according to the manner to be described more fully later on.

In the case of bullet wounds, the common order of procedure is often violated in order to trace definitely the course of the bullet, as well as to recover the bullet itself, if it be present in the body, because of its importance in the eyes of the law as the *corpus delicti*, as well as because of the relation of its size to the caliber of firearms that may be found upon persons connected in some way with the shooting. When a bullet wound has produced extensive hemorrhage into a large cavity, such as the peritoneal or the pleural cavity, the blood should be first completely removed, and the blood-clots, as well as the interior of the cavity, examined for the presence of the bullet. If the bullet is not found there, then its course through the tissues must be followed by locating the various wounds produced, and, generally speaking, no organ should be removed until it is definitely settled that its removal does not in any way obscure the conditions. The best rule to follow in these cases is to trace the bullet to its final resting-place, or as far as possible toward that point, before removing or incising any organs.

It should be remembered that bullets entering the body about the face may be swallowed; and that in bullet wounds in the abdomen it occasionally happens that the bullet is arrested in the lumen of the intestine and carried along by the fecal current.

The Cranial Cavity.—The body now lies upon the back, with the head at the end of the table, the neck and occiput resting upon a wooden block which brings the head well forward. The hair, especially when long, must be parted along the intended line of incision, which runs from the apex of the mastoid process behind one ear over the vertex,

to a corresponding point on the opposite side. In bald persons the incision may be carried across the vertex further posteriorly, in order better to hide the resulting mutilation. This incision is made by means of one stroke of the knife, dividing all the soft layers down to the periosteum. The scalp, by means of dissection and by traction with the fingers, is then reflected on each side of the incision, anteriorly as far as the supra-orbital ridges, the flap being folded over the face; and posteriorly down a little below the external occipital protuberance, the flap being then placed under the occiput. Laterally, the scalp should be loosened down to the external auditory canals. The exposed skull-cap is now removed by means of the saw. The incision should follow the greatest circumference of the skull, passing anteriorly through the glabella and posteriorly through the occipital protuberance, and along corresponding points to the right and left. This line may be mapped out beforehand by means of the knife, and it is always well to incise the temporal fascia and muscles down to the bone along the proposed saw-cut. Many prefer to remove the skull-cap by an incision which runs on each side of the center of the forehead to the base of the mastoid process, and from these points backward and upward to a point a little above the external occipital protuberance, thus removing a wedge-shaped segment of the calvaria. The circular incision is to be preferred because it facilitates certain important cranial measurements.

When beginning to saw the examiner should stand to the left of the body; the incision should be started in the region of the glabella, and, while sawing with the right hand, the left is applied on the anterior part of the scalp, covering the face and steadying the head, which is gradually turned to the left as the sawing proceeds along the right side as far as possible. When the incision cannot be carried any further posteriorly, the saw is lifted out and the head twisted as far to the right as possible, and in this position the sawing is then completed.

The saw furrow should be continuous and even, and great care should be exercised not to injure the pachymeninx or the brain. In medicolegal cases the skull should be sawed completely through all around, so as to avoid entirely the use of the mallet and chisel, which might produce, or be alleged to produce, misleading fractures. The calvaria are loosened by inserting a chisel or cross-bar into the saw-cut and turning the instrument on its long axis. After this the skull-cap may be jerked away from the dura by means of the fingers or a blunt hook inserted underneath its margins anteriorly. If the fingers are used, great care must be taken lest the skin be scratched.

If the dura be so unusually adherent to the skull that traction seems liable to cause injury to the brain, then the membrane must be divided along the saw-cut with probe-pointed scissors; and after cutting the falx cerebri across at its anterior attachment the calvaria and dura are removed together, the falx being also severed at its posterior end. The same procedure may be used in the case of quite young children in whom the dura and skull are still intimately adherent.

The greatest circumference of the skull-cap may now be measured by

placing a tape-line along the sawed margin, and the length determined as well as the width, the latter measurement running at right angles across the center of the long diameter. Other diameters and measurements can also be taken. The form of the skull-cap, the thickness of the bone, the quantity of diploë, the sutures, etc., are now examined.

The exposed surface of the dura is then inspected. The degree of tension should be tested by pinching up a fold near the apex of the frontal lobes; the longitudinal sinus is incised, and its contents examined. The next step consists in dividing the dura on each side along the sawed edge of the skull, from the anterior to the posterior extremity of the falx cerebri, with the point of a scalpel or small scissors, using great care not to puncture the pia. The dura over each half of the convexity is then folded in turn over upon the opposite half, so as to expose the under surface to full view; abnormal contents of the subdural space are now readily seen. If adhesions are found between the pia and the dura, then the corresponding dural area should be cut away and allowed to remain adherent, because forcible detachment might injure the subjacent cortex. The falx cerebri is severed near its attachment to the crista galli, and the dura turned backward at the same time that the pial (superior cerebral) veins emptying into the longitudinal sinus are either torn or, preferably, cut across; the dura is left hanging at the occiput. The color, vascularity, etc., of the pia are now readily made out, and the brain is removed from its cavity in the following manner:

Place the block under the neck, so that the head hangs backward a little; pass the fingers of the left hand between the skull and the frontal lobes, and gently draw these backward. As the brain mass slowly leaves the cavity by its own weight, supported all the time by the left hand, everything that connects the brain with the base of the skull is divided—to wit: the olfactory nerves, the optic nerves, the carotid vessels, the peduncle of the hypophysis, and the third, fourth, and sixth nerves. When the tentorium cerebelli is reached, it is cut with the point of the knife along its attachment to the superior margin of the petrous portion of the temporal bone, great caution being used not to damage the cerebellum. Before cutting any blood-vessels cerebrospinal fluid can be collected with pipets, and as much as possible secured in case chemical examination for either wood or grain alcohol is desired, tests for syphilis, cultures, etc. Then the fifth, seventh, eighth, ninth, tenth, eleventh, and twelfth nerves, as well as the vertebral arteries, are cut. The only remaining connection of the brain is that with the spinal cord, from which it should be divided as nearly at right angles as possible by means of the sharp myelotome. When an ordinary scalpel is used the handle should be elevated as much as possible, and the division made with one precise stroke of the knife. This division should always be made as far below the medulla as practicable. While the left hand supports the brain as before, the fingers of the right hand are placed upon the ventral surface of the cerebellum, and the whole mass is allowed to fall, or is raised, out of the cranial cavity, weighed, and placed with the convexity downward upon a suitable plate.

The base of the skull is now examined, the dural sinuses are incised and inspected, and the pachymeninx is loosened and removed so that the inner surface of the bones may be inspected for fractures and other lesions. The hypophysis may be removed from the sella turcica by carefully cutting away the dural diaphragm which covers this cavity.

The Brain.—The basal leptomeninx, the cerebral nerves, and the basal vessels are examined while the brain lies upon its convex surface. The basal arteries require careful examination because of the frequent occurrence of arteriosclerosis, embolism, thrombosis, etc.; they should be dissected free from the leptomeninx, the layer of the arachnoid which bridges the sylvian fissure incised, and the temporosphenoid separated with the fingers from the parietal lobes, so as to expose the middle cerebral arteries throughout their whole course. The frontal lobes should be separated so as to bring into view the anterior cerebral vessels as they curve over the corpus callosum, and the posterior cerebral vessels traced backward between the cerebellum and the occipital lobes. The arteries may be cut across or opened longitudinally here and there, in order to determine their contents and the condition of their walls.

The brain is then turned over, and a systematic study is made of its general contour, fissure formation, and peculiarities of the cerebral surface. All pathologic areas in the leptomeninx, as well as in the brain itself, are carefully examined and exactly localized. The localization of surface lesions is made easier by the use of outlines of the brain upon which the topography of areas of disease may be indicated. Whenever necessary, the pia may be detached, but it should not be stripped off from areas of the cortex that are to be examined microscopically because of the tearing out of vessels entering and leaving the brain, necessarily disturbing the cortical structure. To remove the pia completely, which may be advisable in order better to study the exact size and form of the convolutions, the artery of the corpus callosum is cut across in front and at the posterior border; the intermediate part is grasped with forceps, and the membrane detached little by little. When sufficient has been loosened to permit it, the free part may be grasped with one hand, which continues the stripping, while the other pushes the brain away from the pia. Should the membrane tear, it should be picked up again with forceps at the bottom of a sulcus in which run the large and strong vessels.

The methods of sectioning the brain are numerous, and it is not possible to recommend any one method as the most suitable under all circumstances. In medicolegal cases in which it is necessary to determine at once the presence or absence within the brain of actual or contributing causes of death the more mutilating methods, by which the brain is cut into very small pieces, may be used. When it is not necessary to subdivide the brain minutely, or when it is to be fixed and hardened and subsequently examined microscopically, then the division into transverse sections is a very satisfactory way of examining this organ, either in the fresh state or after it has been hardened in Müller's fluid,

solutions of formalin, or by embalming with formaldehyd¹ through one carotid artery before opening the cranial cavity. The following method will answer in almost all cases:

The brain is first divided into three parts, one including the pons, medulla, and cerebellum, and the remaining two of the cerebral hemispheres. This division is accomplished by dividing the cerebral peduncles transversely anteriorly to the corpora quadrigemina, and then removing the pons, etc., and by separating the two hemispheres from each other by a median sagittal section through the optic chiasm, the infundibulum, the tuber cinereum, the posterior perforated space, the septum pellucidum, and the commissures of the third ventricle and the corpus callosum. The hemispheres can now be divided into transverse sections

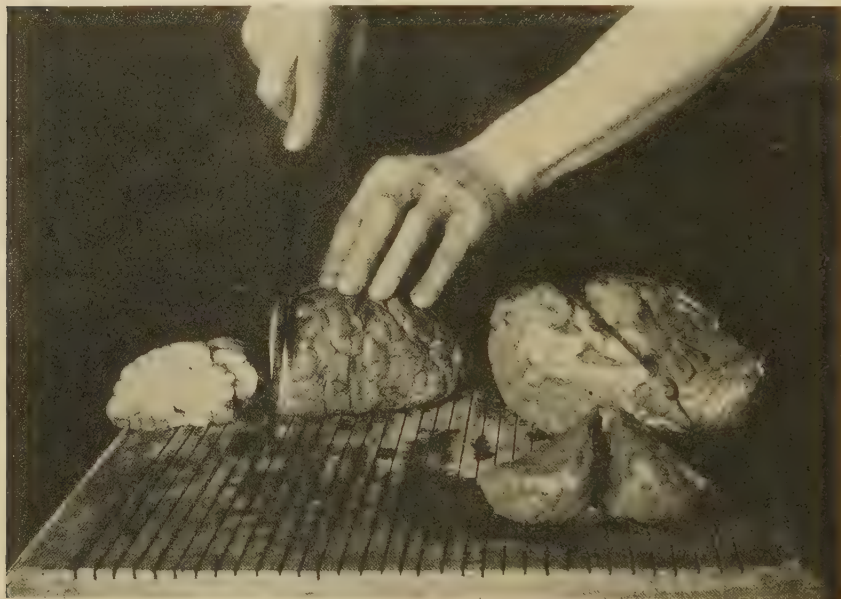


FIG. 15.—Board fitted with parallel grooves, 1 cm. apart, for the purpose of dividing the brain into transverse sections as recommended by Henschen.

according to different plans. A board about 35 or 40 cm. (13 to 16 in.) square, with the surface divided into a number—at least 25—of parallel furrows exactly 1 cm. (0.39 in.) apart (Fig. 15) may be used (Henschen). Placing the hemisphere with the median surface down and at right angles to the furrows, it can be nicely separated into transverse sections exactly 1 cm. (0.39 in.) or more thick, as the case may be, the knife being guided by the furrows in which the point is to be held.

By this plan is secured a sufficiently minute subdivision for gross

¹ A brain kept but a few days in 5 or 10 per cent. solutions of formalin (40 per cent. solution of formaldehyd) acquires a most suitable consistence for handling, but still better results are obtained by embalming with 10 per cent. formalin through the arteries, and this may be easily done after the brain is removed.

purposes, as the size of the ventricles, their lining and contents, as well as foci and tracts of disease, are well displayed, at the same time preserving the topographic relations; and the sections, when hardened, remain serviceable for microscopic purposes.

The above method is recommendable for formalin brains; in the case of fresh brains the sections had better be made 2 cm. (0.79 in.) thick. In hardening a brain which has been divided when fresh in this manner, care must be taken to protect the sections by means of absorbent cotton against bending or distortion from mutual pressure.

According to the method of Pietres, the transverse sections run parallel to the central fissure, and are consequently not exactly transverse to the long brain axis. The hemisphere is placed upon its median surface and fixed with the left hand, while the following sections are made parallel to the central fissure:

1. The prefrontal section through the anterior half of the third frontal convolution.

2. The pediculofrontal section, about 2 cm. (0.79 in.) in front of the central fissure.

3. The frontal section through the anterior central convolution.

4. The parietal section through the posterior central convolution.

5. The pediculoparietal section, about 3 cm. (1.18 in.) behind the central fissure.

6. The occipital section across the occipital lobe.

When the hemispheres are divided from before backward, according to either of these plans, the sections of each hemisphere may be placed in parallel rows upon a plate or tray with the posterior surfaces upward, thus presenting a good opportunity to compare corresponding points in the two halves of the brain.

The cerebellum is examined in this manner: A sagittal section is made through the center of the vermis by means of which the fourth ventricle is also opened, then the restiform bodies and the processus cerebelli ad corpora quadrigemina et ad pontem are divided on each side vertically to their long axes, whereby the cerebellar hemispheres are loosened completely. Each hemisphere is then divided by a horizontal section, starting from the cut surface of the vermis, into an upper and a lower half, thus exposing the nucleus dentatus.

The pons and medulla are divided into three or four segments by complete and exactly transverse incisions which expose their interior sufficiently, at the same time leaving the structures in proper condition for hardening and microscopic examination.

The cerebral hemispheres can also be examined by means of a series of horizontal incisions, according to the old method introduced by Virchow. A brain incised in this manner is less favorable for subsequent microscopic examination with a view to studying and tracing the lesions topographically.

The whole brain lies base downward, and the two hemispheres are separated until the corpus callosum is exposed; placing the left hand on the left hemisphere, the thumb on the median aspect, and lifting the

hemisphere up, a vertical incision is made into the roof of the ventricle in the angle formed by the junction of the corpus callosum with the median surface of the hemisphere, thus opening the ventricle fully. The posterior horn is opened by cutting backward and outward into the occipital lobe; and the anterior by dividing the frontal lobe in a direction a little outward and forward, and then connecting the extremities of these incisions by a nearly vertical cut outside of the basal ganglia, through the floor of the ventricle, and down to, but not quite through, the cortex of the inferior surface. The same incisions are made on the right side, and both lateral ventricles are now fully exposed. The corpus callosum, which has been kept in the median line during these manipulations, is now raised up with the left hand and a knife-point entered through the foramen of Monro, which divides the corpus callosum in a direction forward and upward; the parts behind this division are raised up and turned back, uncovering the velum interpositum and its plexus, which are also carefully lifted up, exposing the third ventricle. A vertical incision is next made into the center of the vermis, opening the fourth ventricle, so that now the entire series of encephalic cavities are open to inspection.

The cerebrum is further examined by dividing the left hemisphere, supported by the left hand, into two equal halves from before backward by means of a long incision that extends down to, but not through, the cortex; and each resulting wedge-shaped half is again bisected in the same manner until the subdivision is regarded as sufficiently minute. The same incisions are made into the right hemisphere. The basal ganglia are laid open by a series of radiating incisions, the common point of origin of which is the cerebral peduncle on each, whence the cuts radiate like the ribs of a fan.

The cerebellum, pons, and medulla are best examined as before described.

The Spinal Column and Cord.—The body lies prone, the neck and upper part of the chest resting upon a wooden block. A continuous incision is made from the occipital protuberance along the spines of the vertebræ down to the center of the sacrum, and the skin and subcutaneous tissue are dissected loose for a short distance on each side of the median line. Deep incisions are now made into the muscle, and all soft parts are dissected away from the laminæ, so that the vertebral arches are fully exposed. Then the laminæ are sawed through near the articular processes, so as to open the spinal canal. This is readily accomplished with the adjustable, double-bladed vertebral saw, the handle being held in the right hand, the left hand pressing the saw against the bones. A single-bladed saw, curved and rounded at the point, also answers very well, and is perhaps a little safer, as it is not so liable to impaction (Fig. 13).

The entire posterior archway should be sawed through, so that every spinous process is readily movable. On account of the greater curvature of the cervical vertebræ, this part, usually requires special attention before the arches are severed completely. Then the ligaments

between the last lumbar vertebra and the sacrum are cut across, and all the arches, held together by the ligamenta subflava, may be removed in one continuous chain by means of a strong forceps. The spinal canal should be opened in this manner only, and without the use of the mallet and chisel. Van Gieson showed that there is great danger of indirect mechanical disturbance of the substance of the cord when the usual violent procedures are resorted to, to say nothing about the liability of directly crushing the cord. In young children the arches may be cut through by means of bone scissors.

In some pathologic institutes the cord is taken out from the front after removal of the vertebral bodies by means of Brunetti's chisel, the pointed guard of which is inserted into the vertebral canal between two pedicles, the cutting-edge resting against the upper pedicle, and the long axis being parallel to the vertebral column; the pedicles are then cut off on both sides by means of blows from the mallet. In this manner the cord is expeditiously removed through the long anterior incision after the organs have been taken out, and the method, therefore, may be of advantage in limited or private autopsies, but there remains some risk of mechanically injuring the cord.

After the removal of the arches the posterior surface of the dura is incised in the median line. The spinal nerves are then cut across with a small scalpel as far out into the intervertebral foramina and away from the dura as possible, while the cord is held out of the way by means of forceps grasping the dura. Moderate traction upon the dura will usually lift the intervertebral ganglia out so that the nerves can be severed peripherally to the ganglia. Then the branches of the cauda equina are cut across, and, while lifting the cord with forceps holding the dura, the attachments between the dura and the canal are rapidly severed. Lastly, the entire circumference of the dura is cut away from the margin of the foramen magnum and the cord lifted out upon a suitable board or tray. During these manipulations great care must be taken not to bend, twist, or compress the cord, which should not be grasped directly, but held by forceps pinching the dura.

The cord is now examined more thoroughly, and, by means of a sharp, thin, clean knife, cut into transverse sections about 2 cm. (0.79 in.) or so in length; the division between each segment should be complete, otherwise there will be traction upon the uncut nerve-fibers, and the division should always pass between two pairs of nerve roots. There is no danger of the segments falling apart, because they are held together by the dura. As the sections are made, care should be taken that the cord is not compressed.

Subsequently, or before incised, the cord may be hardened in 4 per cent. formaldehyd solution (10 per cent. of the commercial article) by suspending it by one end from a cork floating on the liquid in a high bottle, some kind of a weight being attached to the lower extremity.

After the removal of the cord the structures composing the canal are examined for fractures, dislocations, etc.

The Orbits.—On account of its thinness, the roof of the orbital

cavities is easily chiseled away, and the contents of the cavities can be thoroughly examined without any deformity being visible anteriorly. Even the posterior half of the eyeball may be cut away, and the remaining part of the eye kept in place by plugging the orbit with cotton. When demanded, or when there is no objection on account of cosmetic reasons, the eyeball may be removed *in toto*, either from above or through the palpebral fissure.

The Ears.—The ear may be opened *in loco* by chiseling away the roof of the tympanum, going backward so far as to open also the mastoid cells. When it is necessary to remove the ear completely, the incision for removing the scalp is prolonged down upon the neck, the skin and subcutaneous tissue are dissected loose, and the external auditory canal is cut across. The dissection is continued anteriorly as far as the middle of the zygoma and the angle of the jaw, and posteriorly toward the middle of the occiput; the petrous portion of the temporal bone is now loosened by two saw-cuts that meet at its apex and diverge externally, so as to include the mastoid process. The bone is now turned forcibly outward, the temporomaxillary joint usually being opened, and the remaining soft tissues cut across.

The ear may be further examined at leisure according to methods described in special works.

The Nasal and Accessory Cavities.—The best method for examining the nose and its accessory cavities is that described by Harke. After removing the brain in the ordinary manner, the soft parts are reflected anteriorly down to the supra-orbital margins and the root of the nose, and posteriorly down below the foramen magnum. This requires that the incisions for removing the scalp be prolonged on each side along the sternomastoid muscle to about the middle of the neck; then the skull is divided with the saw into two equal parts in the median line, sawing from behind forward, through the occipital bone, the sella turcica, the body of the sphenoid bone, and the ethmoid and frontal bones. The halves are pressed apart by means of a strong effort, aided by the hammer and chisel when necessary on account of resistance in the region of the foramen magnum.

As the skull is forced apart the nasal bones, the hard palate, and the alveolar process of the superior maxillary bone are fractured, but without injury to the soft parts. The frontal and sphenoid sinuses, the nasal passages, and the septum are now readily inspected; bacteriologic inoculations may be made and pieces removed. Usually the median incision passes a little to one side, so that the partitions between the cavities have to be removed with forceps and strong scissors, and in this manner the maxillary sinuses are also opened sufficiently.

When the two halves of the skull are folded together again, the face assumes its usual appearance, and the incisions upon the neck are situated so far posteriorly that when sutured they are not easily visible as the body lies in the coffin.

Opening the Cavities of the Trunk.—The body lies on the back, and the head should hang over the end of the table so as to bring the

neck well forward. The examiner stands to the right of the body, and makes an incision from the hyoid bone to the pubes, passing to the left of the navel. This incision is made with the whole edge of the section knife, which is held nearly horizontally. In many cases it may appear advisable to begin the incision a little lower in the neck, in order to avoid any visible disfigurement. The soft covering of the thorax is at once cut through to the bone, while over the abdomen the primary incision extends only into the subcutaneous tissue or muscles. An opening is then made into the abdominal cavity, just below the ensiform cartilage, and two fingers are passed in; with these the wall is lifted up, and, as the fingers are spread apart, the volar surfaces being directed toward the pelvis, the tissues are divided between them down to the symphysis



FIG. 16.—The body cavities opened and the sternum removed.

pubis. In order to turn the abdominal walls more easily to the side, the recti muscles are severed subcutaneously near their pubic attachments (Fig. 16). In the case of laparotomy having been done the incision into the abdominal wall should pass to one side of the laparotomy wound, in order better to observe the relations between the intestines and the sutures.

On opening the abdomen the escape of gas or fluid must be noted; the latter may be collected and measured, in order to prevent its continuous escape, if present in large quantities.

The abdominal wall is now pulled outward over the costal arch with the left hand, and the soft parts are rapidly cut across from the xiphoid appendix outward to the last rib on each side. This is followed by the loosening of the soft tissues over the sternum and the costal cartilages;

the left hand pulls the covering firmly away from the chest wall, while the deep attachments are divided by long sweeping incisions that pass from below upward and outward. The soft parts are dissected in this manner on both sides beyond the costochondral junctions and up to the superior thoracic aperture. During this process the mammary glands may be incised and examined from behind. In the neck the lower ends of the sternocleidomastoid muscles are cut across and the cellular tissue under these muscles divided on each side, if possible, as high up as the hyoid bone.

A general inspection of the abdominal cavity should be made at this time, in order to avoid any possible change in the position of the organs, or mixture of fluids that might ensue after opening the thorax. In some cases—as, for instance, poisoning or gunshot wounds of the intestines or perforation peritonitis—it is well to finish the examination of the abdominal organs first in order to clear up all the problems under the most simple and favorable conditions. In such cases the general order of procedure is modified as found necessary in consequence of the special conditions of the single case.

Inspection of the abdominal cavity includes a thorough investigation in regard to the contents of the cavity, the color and condition of the peritoneal surfaces, the presence or absence of conditions due to maldevelopment of the peritoneum, the position of the organs, abnormal adhesions, hernias, intestinal malposition and obstructions, etc. When intestinal perforation is suspected the whole gastro-intestinal tract should be examined minutely until it is settled as to the presence or absence of perforation. The tissues close about the abdominal portion of the aorta should be examined for enlarged lymph-glands, abnormalities of the renal veins or arteries, double ureters, etc. Finally the position of the diaphragm is determined by inserting the hand under the costal arches up to the highest point, and then pressing the fingers against the chest wall, when the height is read off with reference to a rib or interspace; the same point should be selected on both sides. In this way information is obtained in regard to the degree of distention of the pleural cavities.

The chest is next opened by dividing the cartilages from the second to the tenth rib, at a point about 0.5 or 1 cm. (0.195 or 0.39 in.) inside of the costochondral junction. The knife is held horizontally, so that as one cartilage is cut the edge rests immediately on the next; in this way the cartilages are cut rapidly without removing the knife from the chest wall and without any danger of injury to the organs of the thorax. When the cartilages are calcified they are divided with an ordinary saw or heavy cartilage forceps. In cases of suspected pneumothorax a small pocket should first be made in the soft parts over an intercostal space, and this filled with water. The sternum is now lifted up with the left hand, the insertion of the diaphragm divided close to the bone, and the cellular tissue of the anterior mediastinum rapidly cut through up to the lower margin of the cartilages of the first ribs. These are divided with a pointed knife from below, and a little farther away

from the sternum than where the second cartilages were severed, great care being taken not to incise the subjacent large veins. The sternum can now be raised toward the neck, and the capsules of the sternoclavicular articulations incised from below, first on one side and then on the other, after which the remaining structures and ligaments are cut easily and the manubrium completely liberated. If too much force is used in lifting up the sternum, fracture of the manubrium may result near or at the junction with the middle piece. Often this junction is a synchondrosis or pseudojoint with slight mobility normally. By grasping the clavicle and moving it the exact location of the sternoclavicular joint is easily determined.

The Organs of the Neck.—In medicolegal cases a painstaking examination of the structures of the neck is necessary, especially when death is thought to have resulted from drowning or strangulation, or when suspicious external marks are observed.

A "cuff" may be made of the skin of the neck by a transverse incision just below the level of where the top of a collar or other dressing of the neck is placed about it for burial. This incision is from the back border of each sternomastoid muscle about their middles, curved down a little, meeting the vertical midline incision made to open the trunk. The skin of the neck from this transverse incision is dissected upward and drawn tightly over the face. When the dissection has been carried in the midline so as to expose a little of the front of the mandible at its middle, the "cuff" will usually lie on the face and out of the way. If it is desirable for special reasons, the dissection of the skin may be carried still further so as to expose all of the front of the mandible, the mandible sawed in two in the midline and spread widely apart at the point of sawing. This facilitates exposure of the mouth and nasopharynx.

First, the thyroid gland should be loosened from the surrounding muscles, its size and form determined, and its interior exposed by converging incisions through each lobe, from above downward. Then the large vessels and nerves, as well as the lymphatic glands and eventually the thoracic duct, are isolated. Simultaneously the deep muscles and other structures may be investigated for bruises and extravasations. In case of hanging, or strangulation by other means, ecchymoses are occasionally found in the intima of the carotid arteries and jugular veins. After completing this dissection the trachea and larynx may be opened in the median line from below upward by means of the point of the scalpel. If the cartilages are calcified, the bone scissors are used, which are also necessary to divide the hyoid bone. The contents of the trachea and larynx are open to inspection before being disturbed during the removal of the organs; the finger may be inserted carefully in order to detect possible foreign bodies in the entrance to the larynx or in the pharynx.

The tongue and the pharynx are removed by passing a scalpel into the mouth from below at the right or the left angle of the jaw, along the inner surface of the bone, and then cutting round to the opposite

angle in close apposition to the bone. The tongue is then brought out below the mandible, and pulled downward with the left hand, the attachment of the soft to the hard palate divided, the cuts going above the tonsils, and the posterior pharyngeal wall incised transversely against the spinal column. Downward traction on the tongue enables one readily to separate the retropharyngeal connective tissue, and the connections between the esophagus and the spine yield very readily, so that the organs of the neck are now freed down to the superior opening of the thorax.

The enterotome is now inserted into the previous incision into the trachea and larynx, and the epiglottis [note the form of the epiglottis before dividing] and the tongue divided in two along the median line. Then the soft palate is divided on one side of the uvula, and the esophagus along its median line posteriorly down to the opening into the thorax. All parts and recesses of the pharyngolaryngeal mucous membrane are now fully exposed; the tonsils can be incised; the ary-epiglottic folds are inspected for edema or wrinkling due to a more or less completely subsided edema; small bodies are detected; and the color and condition of the mucous membrane in general are ascertained. The organs of the neck are then dropped back into the body, or sewed back into their place on each side by stitching the tissues to the angles of the mandible.

The Organs of the Thorax.—Before proceeding to examine the lungs and the heart, the condition of the thymus gland, the mediastinum, the contents of the pleural cavities, as well as the condition of the pleura must be ascertained.

The Lungs.—When adhesions exist between the parietal and visceral pleuræ, these are torn with the fingers or cut across with the knife; very extensive and firm adhesions require the removal of the parietal pleura with the lung, which is best accomplished by blunt dissection with the fingers, separating the extrapleural cellular tissue. Inseparable adhesions between the lung and the diaphragm or the pericardium necessitate the cutting loose of the adherent parts of these structures and their removal with the lung.

After completely separating all adhesions, the lungs may be removed entirely by cutting across the bronchi and the vessels at the root of each, being careful not to wound the aorta, pericardium, or esophagus. In order to incise the lungs, each is placed upon its diaphragmatic surface, the root being held by the left hand, and a free incision made from base to apex, so as to make the largest possible surfaces. It is frequently of great service to distend the lungs with air as a part of their routine examination. This is readily done by a hand rubber-bulb pump to which there is a rubber hose attached and a glass tube to fit the bronchi for the end of the hose.

It is often desirable to leave the lungs attached and to remove the organs of the neck and chest *in toto* because of the continuity of the structures composing them, and of the clearer idea thus obtainable of various morbid processes; the heart, however, is usually separated

in order better to examine and to weigh it. In this case the lungs are incised in the following manner:

The right lung is brought out, placed upon the right chest wall, and held with the left hand so that the median surface presents. An incision is then made with the brain knife, running about 2 cm. (0.79 in.) inside the anterior margin, and extending through the whole lung to its posterior surface, where enough substance is left intact to hold the organ together. This incision divides all three lobes into equal halves. Further, secondary incisions may be made in the direction of the bronchial branches. The left lung is incised in the same manner by placing it upon the left half of the chest wall and holding the anterior margin away from the examiner with the left hand.

The **pericardium** is opened by a small incision in the center of the anterior surface, a small fold being pinched up in order to prevent injury to the heart; this incision is then prolonged downward to the left and to the right, and upward as far as the reflection of the membrane upon the large vessels; the contents and the surface of the sac are now examined. In case circumscribed adhesions exist, they are to be divided with the knife; if the cavity be completely obliterated, a separation may be accomplished by blunt dissection with the fingers; or it may be necessary, in some cases, to remove the pericardium with the heart, and to make the necessary incisions into the heart cavities through the pericardium and the heart wall at the same time.

The Thymic Body.—The vertical incision of the pericardium is prolonged up and to the right with a similar incision of the left side, each as far as it is possible, still incising the pericardial sac. With this flap of pericardium the thymic body is dissected up, holding the flap vertically and taking care not to wound the left innominate vein or superior vena cava, and prolonging the dissection to the lower margin of the thyroid gland. In many cases it is desirable to remove the thymic body and expose the large vessels, and to examine these vessels with the vessels of the neck before any other examination is made of the neck.

The Heart.—This can be examined according to various plans, each of which, when understood, yields satisfactory results, the fundamental principle in all methods being that each step in the procedure must not in any way interfere with the parts that remain to be examined. External inspection of the heart reveals its position, size, and form, as well as the condition of the coronary vessels. A marked distention of the veins upon the anterior surface of the heart points to obstruction to the outflow from the right auricle, and is consequently observed in cases of asphyxia.

In order to determine the amount and the condition of the blood contained in each, the various chambers of the heart are best opened while it is *in situ*. The incisions for this purpose are made in such fixed locations as to serve as the beginning for those incisions employed in the more detailed examination after its removal. In order to determine the weight of the heart and the sufficiency of its valves, it is

always best to remove it, although many pathologists complete their examination of the organ while it remains *in situ*; others remove it unopened.

Place the left hand under the heart and draw it downward and to the left, make a vertical incision with blunt-pointed scissors into the pulmonary conus, and extend this distally into the pulmonary artery. This part of the examination is to be carried out with as little handling of the heart as possible before it is greatly disturbed in any way so as to allow the contents of the pulmonary artery and its two branches to be examined, for emboli lodged in them may be loosened or have their location changed unless this examination is made early before the organs of the thorax in general have been much disturbed. This is especially

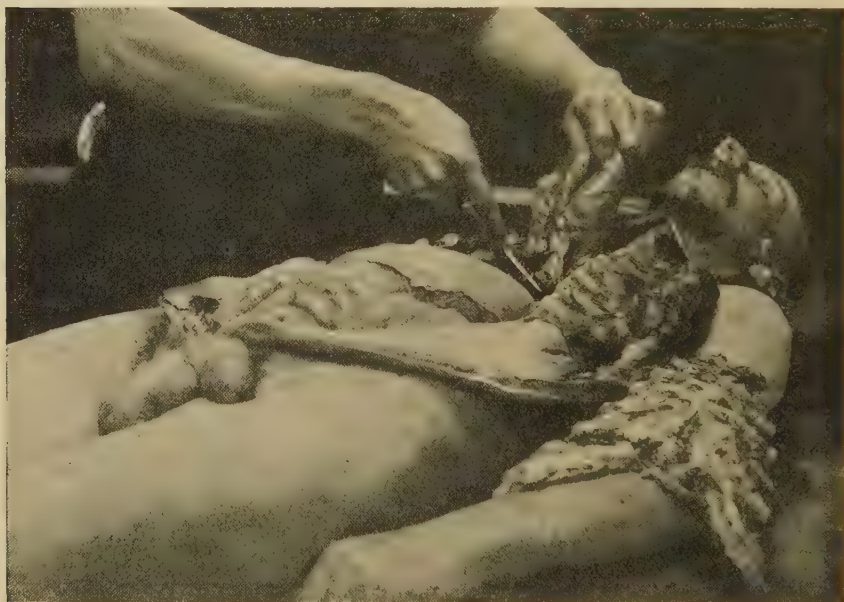


FIG. 17.—Removal of the heart.

necessary with sudden death and particularly in puerperal women. Then an incision is made into the right auricle, between the entrances of the superior and the inferior vena cava. Then open the right ventricle by an incision beginning below the circular furrow, and running downward to near the apex, along the right margin and in line with the cut made into the auricle; the contents of these cavities may now be examined.

To incise the cavities of the left side, grasp the heart so that the fingers of the left hand lie upon the anterior surface and the thumb upon the posterior, the apex resting in the hollow of the hand. Make an incision from the left superior pulmonary vein through the auricular wall nearly down to the transverse furrow, and then another into the

cavity of the left ventricle, commencing below the transverse furrow and extending along the left margin down to the apex. The contents of these cavities are now removed and examined.

Next, the heart is removed by lifting it directly upward and cutting successively the vessels that enter and leave it, as near to the pericardium as possible (Fig. 17). The competency of the semilunar valves is next tested with water; all coagula are removed, the aorta and pulmonary artery are trimmed down, so that the behavior of the valves can be observed as the water is poured into the vessels, while the heart



FIG. 18.—Opening the right ventricle by cutting along the interventricular septum, the blunt point of the scissors projecting from the pulmonary artery.

is suspended by the auricles so that the plane of the orifices is horizontal. Competent valves meet exactly under the column of water, whereas the segments of incompetent valves fail to meet and allow the water to trickle away.

The heart is now opened completely by passing the blunt end of an enterotome into the right ventricle, ventral to the attachment of the papillary muscle to the anterior wall, and cutting through the wall as much to the left as possible, continuing the incision out through the pulmonary artery (Fig. 18); it will be found that when the scissors are

held as far to the left as the septum between the ventricle permits, the division will pass between two valve segments without injury to either (Fig. 19).

The left ventricle is opened by passing the enterotome upward into the cavity from the incision already made, cutting along the interventricular septum (Fig. 20), and then between the pulmonary artery and the auricle, through the aorta; one of the aortic segments is unavoidably cut in two by this incision.

The auricles may be opened still more by prolonging the incisions made out through the veins on each side, a good view being thus obtained of their interior and also of the auricular aspect of the mitral



FIG. 19.—Right ventricle laid open, as shown in Fig. 18, and without cutting papillary muscle attached to anterior wall.

and tricuspid valves. Finally, the original incisions into the auricles and ventricles on each side may, if desirable, be united by cuts that divide the mitral and tricuspid rings; but these cuts may spoil the characteristic appearance of stenosis of the orifices, as well as other changes.

When it is desired to obtain exact measurements of the size of the orifices of the heart by means of graduated cones, the foregoing procedures are so modified that the cones are inserted into the orifices before the incisions described have divided the semilunar and auriculo-ventricular rings; naturally, these cones are inserted in the same direction as the blood current, and with great gentleness, so as not to detach the inflammatory vegetations and thrombotic deposits. The diameter

of the mitral and tricuspid orifices is often estimated by carefully inserting the fingers from the auricular aspect—in the adult the mitral normally admits three finger-tips; the tricuspid, four. There is, however, a rigor mortis of the heart which may alter these dimensions.

Having removed and opened the heart, the examiner is now ready to make a detailed examination of all its parts. The valvular and the mural endocardium are to be looked over, the foramen ovale and the membranous part of the ventricular septum are inspected, the size of the ventricles as to the depth and thickness of the wall may be measured, while the weight should always be determined, as it gives the



FIG. 20.—Opening the left ventricle by cutting along the interventricular septum, the blunt point of the scissors projecting from the aorta.

most accurate indication of absolute increase or diminution in substance. The condition of the coronary orifices in the commencement of the aorta must be investigated; these orifices may be seriously involved in the sclerotic changes so often found immediately above the aortic valves. In all cases of sudden death from obscure causes the coronary arteries must be searched for arteriosclerotic and other changes, and for this purpose they are cut open from their beginning in the aorta to the smallest branches. In the event of doubtful coronary disease and secondary myocardial changes microscopic examination may show astonishingly extensive lesions. The myocardium,

especially of the left ventricle, is finally exposed by a number of incisions, either parallel with, or vertical to, the surface of the heart.

Having examined the lungs and the heart wholly or partially *in situ*, the remaining thoracic organs and the organs of the neck are removed *in toto*. The left hand grasps the organs of the neck and pulls them downward, the right and left subclavian arteries and veins and other structures are cut across by a curved incision on each side at the superior opening of the chest, and the cellular tissue between the esophagus and the thoracic aorta and the spinal column rapidly separated as far as the diaphragm, while the organs are drawn downward. Then the esophagus is ligated near the diaphragm and divided above the ligature, at which time the aorta, the inferior vena cava, and the parietal pericardium are also cut across. The organs are then placed upon a tray, the esophagus being uppermost. This latter is then divided along the posterior wall, in continuation of the incision already made into it. Turning the mass around, the arch of the aorta and its large branches, as well as the thoracic aorta, are laid open; then the trachea is opened by continuing the incision already made into it, and this opening may be continued into the right bronchus; but in order to open the left bronchus the aorta must first be freed and taken out of the way.

The peribronchial lymphatic glands are also to be incised, and their relation, if perchance tuberculous, to adjacent vessels determined. If necessary, the lungs may be detached and weighed. In the case of aneurysms of the aorta, tumors, and other swellings of the mediastinum caution must be used in removing the organs from the chest, so that instructive specimens are not marred by unskilful dissection, and the relations disturbed.

The Organs of the Abdomen.—A preliminary inspection of the abdominal cavity was made for the purpose of orientation immediately after the long anterior incision; before any of the organs are removed the cavity should again be inspected and the condition of the peritoneum definitely ascertained in all its details.

The Spleen.—This is grasped with the left hand and drawn forward from its position behind the fundus of the stomach, any adhesions present being carefully separated. As it is drawn forward the gastro-splenic omentum is brought into view, and any gross changes in the splenic vessels, the presence of accessory spleens, etc., readily observed. It is then removed by cutting across the structures at the hilus, weighed and measured, and an incision made along the outer surface from the upper to the lower end, additional lamellations being made if necessary.

The region of the **gall-bladder** and **biliary ducts** is to be carefully inspected for adhesions, fistulæ, and other changes. In case jaundice exists, the patency of the common duct is tested in the following manner: By cutting across the diaphragm the liver is allowed to fall into the chest cavity, so as to bring the region of the hepatoduodenal ligament well into view; then the second part of the duodenum is incised

along its anterior surface between two ligatures placed at a liberal distance from each other, and the exposed mucous membrane is wiped dry. Now, by compressing the biliary duct with the fingers and toward the intestine, one can observe whether or not the bile can be expressed, and also its condition as it exudes at the biliary papilla, which is located about 9 cm. (3.5 in.) from the pylorus. Compression of the gall-bladder itself should be avoided until the results of the foregoing procedure are established. The portal vein can also be examined at this time.

Diseases in the region of the gall-bladder, the duodenum, the pylorus, and the pancreas often result in such matting together and in such extensive adhesions that it may be necessary to remove these organs as well as the liver, the stomach, and perhaps the large blood-vessels in conjunction, in order to be able carefully to dissect and examine the complicated conditions satisfactorily. In removing such masses it is necessary first to inspect the conditions *in situ*, and also to examine the surrounding structures that are liable to become injured or disturbed during the removal, such as the right kidney and adrenal; hence such removals *en masse* are to be postponed until the examination of the abdomen is completed.

In cases of hemorrhagic and other forms of pancreatitis, with or without disseminated fat necrosis, the diverticulum of Vater and the ducts that empty into it should be carefully examined for calculi, for Opie has shown that their lodgment in the diverticulum may lead to the regurgitation of bile into the pancreatic ducts.

The **liver** and the **gall-bladder** are removed under ordinary conditions by lifting the liver up, with the left hand grasping its lower margin, and then severing the hepatoduodenal ligament, observing at the same time the cross-section of the blood-vessels and duct which it contains, the ascending vena cava, the suspensory and the coronary ligaments, and the cellular tissue between the right adrenal and the liver. In case firm adhesions exist between the liver and the diaphragm, the corresponding parts of the latter may be removed with the liver. It is then placed on its anterior surface, and the exterior and interior of the gall-bladder examined. The gall-bladder is opened by a longitudinal incision while attached to the liver, or it may be freed by dissection and incised by itself. The larger branches of the portal vein and the part of the inferior vena cava usually removed with the liver are to be laid open. The liver is then weighed and measured, and its interior exposed by a long incision passing transversely through the center of the right and the left lobe; additional transverse incisions may be made parallel to the first.

The **kidneys** and **adrenals** are best examined in the following manner: Beginning with the left side, the sigmoid mesocolon is divided near the intestine, which is placed on the stretch by the left hand and drawn over to the right, so that the left kidney and adrenal are fully uncovered; by a little dissection the beginning of the ureter and the renal vessels are exposed, so that cognizance may be taken of any gross

anomalies or morbid changes. Then the kidney is loosened from its bed by passing the left hand underneath it from the outside and from below upward, aided by the knife if necessary. In order to remove the adrenal with the kidney it must be dissected free from its loose investment before the kidney is lifted out of the body, and as the adrenals, especially in the old, are very friable, they must be handled gently. As the kidney is lifted out of the body the vessels are cut across, but the ureter should remain attached.

The right kidney is removed in the same general way; the cecum and ascending colon are loosened and crowded over to the left, the vessels and the ureter exposed, and the kidney and adrenal separated from their investments and lifted out of the body, the vessels, in the ordinary case, being divided while the ureter remains connected with the renal pelvis. The ureters are readily isolated down to their entrance into the bladder by means of careful traction, aided by a little blunt dissection.

In case of acquired or congenital malposition of the kidneys it may be necessary to deviate from this method, because in floating kidney the great lengthening of the vessels, and in the instances of congenitally fixed dislocations, with or without fusion, the atypical origin and number of the vessels may require a more extensive and painstaking dissection, preceding which the intestines had better be removed.

In the routine case the adrenals are next detached from the kidneys, weighed, and measured, and then incised in the longest diameter in a sagittal direction. Then each kidney is measured and divided into two equal longitudinal halves by an incision from the convex margin to the pelvis. The kidney is held firmly in the left hand, with the hilus in the angle between the thumb and the fingers, the thumb being applied to one surface and the fingers to the opposite aspect, and with one stroke of the long knife the division is made from end to end and down to the hilus; in this manner the kidney is divided into an anterior and a posterior half at the same time that the calices and pelvis are laid open. This division should be a perfectly median one, otherwise the pelvis and calices are not clearly displayed. The fibrous capsule of the kidney is now detached by pinching up the cut margin of the latter at the convex border of the kidney, and stripping it off from the surface; when the capsule is thickened and adherent as a result of chronic inflammation, thin layers of the cortical substance are brought with it. The external surface of the organ is now examined, and then the cut surface, paying particular attention to the cortical markings and the relative thickness of the cortex and the medulla. Normally the thickness of the cortex to that of the medulla is as 1 to 3, the measurement being taken from the apex of a medullary pyramid to the surface of the kidney, bisected by median division. Finally, the mucous membrane of the pelvis is examined and, with probe-pointed scissors, the ureters laid open, from the pelvis to their entrance into the bladder. If it be found there are no anomalies, ascending or descending inflammations, or dilatations, which are best studied when the urinary passages

remain continuous, then the ureters may be cut across and the total weight of the kidneys ascertained.

The **pelvic viscera**, including the bladder, urethra, the sexual apparatus, and the rectum, should all be removed together.

In case it is necessary to examine chemically the contents of the urinary bladder, this may be evacuated with a clean metal catheter; in the case of obstruction to the catheter the bladder may be evacuated by way of a small incision in its anterior surface.

The **rectum** is separated from the descending colon between a double ligature. The bladder is loosened by inserting the fingers between the parietal peritoneum and the posterior surface of the symphysis pubis; then the loose retroperitoneal connective tissue is gradually separated in the same manner on each side from the inner pelvic wall, so that the hand can be passed all around the pelvic organs and behind the rectum. The thighs are now forcibly adducted, and while the external genitalia are grasped and pulled downward with the left hand, a curved incision is made through the skin at the root of the penis, respectively clitoris and the ligamentous structures, and the attachments of the corpora cavernosa divided close to the pubic arch, until the knife freely enters the pelvic cavity. Then the opening is enlarged, and the left hand grasps the external genitalia from within the pelvis, into which they are drawn underneath the pubic arch, while curved cuts, meeting behind the anus, are made through the skin on each side, and the muscular and fibrous tissues on each side and behind the rectum divided until all the attachments of the organs to the pelvis are freed. The pelvic organs are finally lifted up, and the parietal peritoneum divided on a level with the promontory of the sacrum.

If the kidneys have been allowed to remain connected, the examiner now has before him the whole urinary tract in continuity, as well as, in women, the whole, and in men practically the whole, genital tract, and also the rectum. By a little modification of this procedure the vasa deferentia and the testicles may be isolated and guarded from separation during the removal of the pelvic organs, which would be a wise plan in cases of extensive urinary tuberculosis.

In men the further examination consists in opening the bladder along the middle of its anterior wall, and from this incision the anterior wall of the urethra is incised by means of probe-pointed or small intestinal scissors while the penis is held on the stretch, so that the incision does not invalidate the posterior wall and thus mutilate the preparation. The mucous membrane of the bladder and urethra is now fully exposed for examination.

The testicles are bisected in such a manner as to include in the median incision the head of the epididymis.

Now, the rectum is separated from the bladder and the prostate by means of a careful dissection carried along by small cuts in the external layers of the wall of the rectum, beginning in the floor of the rectovesical fossa, while the structures are made tense by traction on the bladder in one direction and on the rectum in the opposite. The

seminal vesicles, the prostate, and Cowper's glands are in this way made accessible to a satisfactory examination.

In women the urinary bladder is opened from the urethra; the vagina and the uterus are divided along the center of their anterior walls by an incision which divides the bladder into two halves, unless it is previously loosened and laid to one side; or the vagina and uterus may be opened along the posterior wall after first removing the rectum. At the upper end of, and at right angles to, the sagittal incision into the uterus two shorter cuts are made toward each uterine opening of the Fallopian tubes. Before opening the uterus the appearance of the external os should be studied in order to obtain information as regards the previous occurrence, or not, of childbirth. The size of the uterine vessels and the thickness of their walls are also to be noted, and in the puerperal uterus additional incisions into the wall, especially at the placental site, may be necessary in order to determine the condition and the contents of the vessels. The Fallopian tubes are cut open with small scissors, the ovaries bisected with a horizontal incision, and the vessels in the parametrium and the broad ligaments examined.

Finally, the rectum is emptied of its contents by means of a stream of water, and opened with the enterotome along the posterior wall.

When external conditions prevent the removal of the external genitalia, the pelvic organs are to be loosened from the pelvis as before, and drawn firmly toward the diaphragm with the left hand, while the right divides with the knife the urethra as far as possible in front of the prostate gland in men, the vagina at its middle in women, and the rectum as low down as possible; the organs are then examined as before.

The **stomach** and **duodenum** may be examined *in situ* by making an incision with the enterotome, or by continuing the incision eventually already made into the duodenum in examining the patency of the bile-ducts, from the pylorus along in the anterior wall, a little below and parallel with the lesser curvature and out through the part of the esophagus that still remains. Care should be taken to empty the stomach before the incision becomes so large that the contents cannot be retained by holding up the margins of the opening. Simultaneously the duodenum, or that part not already exposed, may be examined by cutting it open with the enterotome, the hepatic flexure of the colon, and the transverse colon being first loosened and turned downward.

In the majority of medicolegal cases, and especially when poisoning is not definitely excluded from the start, the stomach and duodenum are to be removed unopened from the body. A ligature is placed around the lower end of the esophagus, the diaphragm being divided so as to expose this part of the esophagus freely, and then the attachments along the lesser and greater curvatures are divided, the duodenum is dissected loose, and a double ligature placed securely at its lower end, between which it is then cut across. After emptying the contents into a suitable jar the organs may be incised as above and the mucous membrane examined.

The Pancreas.—This is exposed by dividing the insertion of the

great omentum to the larger curvature of the stomach, and then separating the transverse colon and the stomach. The pancreas may be incised along its greater diameter while *in situ*, or dissected loose from its attachments, care being exercised that pathologic conditions connected with its duct, or its opening thereof into the duodenum, are not thereby deranged.

The duct is easily entered by an incision across the pancreas at its middle or its tail and inserting a probe, after which it is opened lengthwise. It should be remembered that the duct is in the lower third.

Diseases such as cysts, tumors, abscesses, fistulous passages, etc., in the region of the stomach, duodenum, pancreas, gall-bladder, and liver usually require the removal of these organs *en masse* in order to clear up the conditions by a careful dissection.

The Intestines.—These are best examined, after they have been carefully inspected, together with the mesentery, while *in situ*, by their complete removal from the body and their opening under the faucet or under water, while their contents, when not to be preserved, are allowed to run into the sewer or into a pail. Grasp the lower end of the large intestine, which remains ligated from the time the rectum was removed, and, making it tense, sever all the attachments close to the bowel. When the small intestine is reached, make the mesentery tense with the left hand, which lifts the bowel up, while the right divides the mesentery very close to the bowel by means of an almost continuous sawing motion of the knife, thus allowing the intestinal coils to straighten themselves completely. As the intestines are separated they are allowed to fall either into a pail between the thighs or at the side of the body. This detachment is continued up to the duodenum, where double ligatures are placed, if this has not already been done.

The small intestine is opened along its mesenteric attachment, because the Peyer's patches are situated opposite thereto and may be the seat of important changes; the opening is made by drawing the intestine through a partially opened enterotome held in the right hand, the blunt end, which passes into the bowel, being held downward; and as this process continues, the open part spreads itself out over the fingers of the left hand, allowing one to inspect the contents and mucous membrane at the same time.

When the intestine, not yet incised, becomes coiled and twisted, it is straightened out by lifting the part being cut high in the air, provided it has been separated near or at the mesenteric attachment. Whenever necessary one may wash off the mucous membrane in order to remove the contents sufficiently. When the contents are to be saved they are emptied into a suitable bottle or jar by removing a ligature before incising the intestine; if it be necessary to examine the contents of different parts, then such parts are separately ligated and the contents emptied into different bottles.

The large intestine is incised in the same way, along one of the three longitudinal bands or teniæ, and emptied of its contents so as to expose the mucous membrane.

The intestines may also be opened and examined *in situ*: Beginning immediately above the ileocecal valve the small intestine is incised with the enterotome upon its under surface near the mesenteric attachment. As the left hand turns the coils upward so as to present the under surface, this incision is carried along step by step up to the duodenum, the mucous membrane being examined as the bowel is laid open. When examination of the small intestine is finished, the large intestine is cut open from the ileocecal valve downward along the anterior longitudinal band. If desirable the entire bowel may be removed and weighed before emptying in order to state accurately the weight of its content.

The **retroperitoneal structures**, such as the nerve plexuses, the aorta, the vena cava, and the retroperitoneal lymphatic glands, are made accessible by cutting the mesentery across at its root, splitting the large vessels open, and isolating the nerve plexuses and semilunar ganglia by careful dissection. Another method of examining these structures is mentioned later (see page 117).

The **diaphragm**, the anterior surface of the **spinal column**, and the **pelvis** are now also open to inspection. The various pelvic diameters may be determined and the form of the pelvis studied.

The Extremities.—In the extremities the blood-vessels, nerves, lymph-glands, lymph-vessels, muscles, bones, and joints may require examination in special cases. The location and course of the incisions employed for the purpose of exposing or isolating any of these structures are determined by the anatomic conditions; in some cases the examiner may feel it necessary to conceal the cuts as much as possible. The joints are opened by the familiar incisions used in exarticulations and resection. In order to expose the bone-marrow for general inspection one of the femurs is usually removed and divided longitudinally by means of a saw, the bone being held in a vise. In rachitic and syphilitic children the lines of ossification at the various epiphyses may show characteristic changes from the normal that are best studied upon longitudinal section of the bones.

EXAMINATION IN CASES OF SUSPECTED POISONING¹

In order to preserve the organs and fluids from such cases in proper condition for chemical analysis a number of new, glass-stoppered jars and bottles, thoroughly washed and rinsed with sulphuric acid and finally with distilled water, should be secured. As the organs are placed in the jars these should be sealed and labeled. If they can be delivered to the chemist immediately, then it is unnecessary to add any alcohol; if they are to be kept for a time or sent some distance, a sufficient quantity of strong alcohol must be added. A quantity of the alcohol used is to be poured into a clean, empty bottle, which is then sealed and labeled and sent with the organs; this is done in order that opportunity be given for examination of the alcohol alone, as regards the absence or presence of poisons. If formalin is used a sample of that used should also be sent to the chemist.

¹See chapter on General Principles of Toxicology, page 36.

While such organs remain in the care of the examiner, he must keep them under sealed lock and key so that he can swear, if necessary, that no poisons were added or the material tampered with while under his care. Such jars should be delivered only to some properly authorized person, and an accurate record of the number, contents, the seal, and the disposition of the jars and bottles should be made at the delivery and kept for future use.

What organs and fluids should be preserved will depend largely on circumstances. The stomach and intestines with their contents, the liver, and the brain should always be preserved. In the case of diffusible poisons—strychnin, arsenic, etc.—the urine should be drawn with a clean catheter into a new, clean bottle, and, in addition to the stomach and intestines with their contents, every internal organ and also a mass of muscular tissue and a large piece of bone should be kept, so as to furnish the chemist with sufficient material to make the result of his examination as positive as possible; the urine is important and the cerebrospinal fluid also on account of the grain or wood alcohol they may contain. A portion of the blood should be kept in those cases in which the spectrum analysis may be expected to furnish important information. In cases in which it is known or supposed that the poison was inhaled, the lungs should always be sent to the chemist, because it is possible, for instance, to recover chloroform from the lungs even long after death. Narcotic or convulsive poisonings may be simulated by uremia, or such claims may be advanced, and in cases of suspected intoxication of this nature both kidneys should be secured, partly for chemical and partly for histologic examination; for the latter purpose small pieces may be cut out and fixed in the different solutions used.

The organs and tissues, before they are placed in the jars, are subjected to the same examination as under ordinary circumstances, but much caution is to be used so as not to bring them in contact with possible poisonous substances.

In a case of suspected poisoning the examination should begin with the abdominal cavity, the position and the fulness, color, and smell of the stomach and other abdominal organs being carefully noted. Then a double ligature is placed around the lower end of the esophagus, immediately above its junction with the stomach; the duodenum is tied in two places, the ligatures being placed at a safe distance from each other so they will not slip. The stomach is then removed, the duodenal ligatures cut, and the end of the duodenum placed in a wide jar and the stomach allowed to empty itself.

The small intestine may be removed, and the contents emptied into another jar or bottle; the large intestine may be treated likewise.

The examination of the digestive tract is done at this early time in order to avoid admixture, as well as injury to the stomach and the intestines during the course of the autopsy.

The stomach and the intestines are best preserved by themselves, because poison may cling to the mucous membrane. As to the other

organs, it cannot be said to be absolutely necessary to preserve each organ or set of organs by itself, although this would be the best plan.

In case trichinosis is suspected, the contents of the upper part of the small intestine must be subjected to careful microscopic examination, and pieces are to be taken from the intercostal and cervical muscles and from the diaphragm.

EXAMINATION OF NEWBORN CHILDREN

"In examining the bodies of newborn children we may have to determine, besides the ordinary lesions of disease, the age of the child, whether it was born alive, how long it has been dead, what was the cause of death." The examination consequently requires especial attention to the following features:

1. **Inspection.**—Inspection of the newborn takes into consideration a number of points that bear directly upon the age of the child and the length of time that has elapsed since its birth.

The following table shows the weight and the length of the fetus at each month of gestation (von Hecker):

	Weight.		Length.	
Second month.....	4	gm.....	2.5	to 3 cm. (1 to 1.2 in.)
Third month.....	5.2	".....	7	to 9 " (2.7 to 3.5 ")
Fourth month.....	120	".....	10	to 17 " (4 to 6.8 ")
Fifth month.....	284	".....	18	to 27 " (7.1 to 10.6 ")
Sixth month.....	634	".....	28	to 34 " (11 to 13.4 ")
Seventh month.....	1218	".....	35	to 38 " (14 to 15 ")
Eighth month.....	1549	".....	39	to 41 " (15.4 to 16.1 ")
Ninth month.....	1971	".....	42	to 44 " (16.5 to 17.3 ")
Tenth month.....	2334	".....	45	to 47 " (17.7 to 18.5 ")

From the fifth month the age in months can be estimated by dividing the length in centimeters by five. The pupillary membrane disappears in the eighth month. At full term the skin is quite firm and white; the lanugo is found chiefly on the shoulders; the navel is situated a little below the center of the body; the nasal and aural cartilages are quite firm; the nails reach beyond the fingers' ends, but not beyond the ends of the toes; the labia are nearly always closed, and both testicles should occupy the scrotum.

In addition to determining the length, the weight, and other points referred to, the following measurements may be taken. At term the results are about as given:

The length of the hair.....	1.5	to 3	cm. (0.6 to 1.2 in.)
The length of the anterior fontanel.....	2	to 2.5	" (0.8 to 1 ")
The circumference of the head.....	34	to 44	" (13.4 to 17.3 ")
Mento-occipital diameter.....	33	to 38	" (13 to 15 ")
Fronto-occipital diameter.....	41	to 44	" (16.1 to 17.3 ")
Transverse (parietal eminences) diameter.....	19	to 22	" (7.5 to 8.7 ")
Bitemporal (lower ends of coronal sutures) diameter... ..	8		" (3.2 in.)
Width of shoulders.....	12		" (4.8 ")
Width across trochanters.....	9		" (3.6 ")

At this time it is most convenient to speak of one of the most reliable signs of maturity—namely, the center of ossification in the

lower epiphysis of the femur. In order to examine this center the knee-joint is opened by a transverse or horseshoe-shaped incision between the patella, and the soft parts are dissected away from the lower end of the femur; the epiphyseal cartilage is then divided from below into thin transverse slices until the greatest diameter of the focus of ossification present is reached. This diameter is then accurately measured. It is necessary to divide the cartilage transversely, because only in this way is the greatest diameter encountered. At full term the diameter varies from 2 to 5 cm. (0.8-2 in.); the center is not present until the thirty-seventh week (Fig. 21). The centers of ossification of the sternum are also of importance in estimating the period of development. In still-born children the line of ossification at the junction of the epiphysis with the shaft of one or more long bones must be examined for evidences of congenital syphilitic osteochondritis by dividing the bone longitudinally.



FIG. 21.—Center of ossification in the lower femoral epiphysis at term (Bichat's center).

After birth the skin soon becomes more dense; on the second or third day it assumes a yellowish tinge, which increases to the fourth day. The umbilical cord soon begins to shrivel; it becomes brownish red, and after three or four days the skin around its insertion becomes somewhat red. The end of the cord should be closely inspected to determine whether it is cut or torn. A partially or wholly cicatrized navel, or redness, swelling, and suppuration about the insertion of the still attached cord, is, of course, an absolute proof that the child has lived several days after its birth. Finally, the whole body is to be inspected for marks of violence, blood, evidences of decomposition, etc.; the

orifices, especially the mouth and the nose, are to be examined for foreign bodies.

2. **The Spinal Canal.**—In opening this canal the arches are best cut across by means of a strong pair of scissors.

3. **The Head.**—The incision and deflection of the soft parts are made as in adults. The margins of the bones of the cranium can then be separated from their attachment to the dura as follows: Make a small opening in the center of the anterior fontanel and incise the superior longitudinal sinus; then divide the dura on each side of the sinus; now cut through the dura along the coronal and lambdoidal sutures on each side, carefully avoiding the surface of the brain; the bones of the skull can now be drawn away from the brain and cut through across the greatest circumference, and the brain removed as in the adult. On account of the extreme softness of the brain in children and the firmness of the dural adhesions along the sutures it is very difficult to succeed in removing an infant's brain without some injury. An attempt to saw through the calvaria in the ordinary manner nearly always results in injury to the brain. If it be not desired to remove the brain as a whole, then Griesinger's method of sawing through the skull and the brain at the same time is very serviceable; the calvaria receives the upper part of each hemisphere, and the rest of the brain is removed as in the adult.

4. **The Abdomen.**—In the newborn the examination of the navel and of the umbilical vessels is of great importance. Nauwerck practises the following modification of the ordinary method: The usual incision is made from the chin downward to a short distance above the umbilicus, where this incision divides, as it were, into two diverging incisions that extend to the pubes; the abdomen is opened along the lines thus mapped out, and the triangular flap in the abdominal wall is raised up by traction on the cord or the navel. This makes the umbilical vein prominent. By dividing the vein, after having opened and examined it, the flap is turned down over the pubes, and the umbilical arteries are seen on each side of the urachal remnants and may be examined; or one may make the usual incision to the left of the navel and then excise the navel by a cut around its right aspect, severing the umbilical vein and arteries, and then examine these structures and their contents by means of successive transverse incisions.

5. **The Thorax.**—The ductus arteriosus is best examined *in situ*: the thymus gland is removed; the right ventricle is incised along the interventricular septum, and the cut continued along the middle of the anterior wall of the pulmonary artery; the orifice of the ductus arteriosus will be found midway between and beyond the two openings of the right and the left pulmonary branches, and a small probe may be passed through the duct downward and a little to the left into the aorta.

In order to determine whether or not respiration has taken place, the following procedure is practised: The height of the diaphragm is determined before the chest is opened (when respiration has fully taken place the diaphragm reaches to the fifth or the sixth rib; otherwise only

to the fourth); the trachea is ligated in the neck before opening the chest; then the chest is opened, and the pleuræ, pericardium, and heart are examined; the pharynx, larynx, and trachea, above the ligature, are also opened and examined. The organs of the chest are now removed *in toto*, the trachea being divided above the ligature, the heart and the thymus gland separated, and the lungs placed in a basin of cold, clean water. In case they float freely, respiration has undoubtedly taken place; if the lungs sink, then the test is not decisive. The lungs, under such circumstances, are to be incised and note taken as to whether they crepitate or not, and whether air-bubbles appear when parts are compressed below the surface of the water. Furthermore, the lungs must be separated into lobes, the lobes into minute pieces, and the hydrostatic test again applied. In this way it may be possible to determine that air has gained entrance into certain parts of the lung in sufficient quantity to prevent small pieces from sinking.

In the case of decomposition and the possible production on that account, in the lungs, of sufficient gas to buoy them up in the water, then a number of small pieces from the lungs are to be placed between the folds of a towel, and thoroughly compressed between two flat surfaces, such as between the floor and a board, exerting pressure by standing on the latter. The gas due to decomposition is pressed out, and the pieces from atelectatic, decomposed lungs will sink when thrown in the water after this treatment; inspired air, on the other hand, cannot be pressed out, and the pieces from inflated lungs continue to float.

EXAMINATION OF THE ORGANS FROM BEHIND

Following removal of the spinal cord the trunk may be opened from behind, removing the ribs far out on each side as well as the thoracic, lumbar, and sacral portions of the spine. This method is not usually employed except when it is desired to learn unusual topographic alterations, such as conditions of displacement, etc., in the thorax, for example, from mitral stenosis and enlargement of the left auricle.

Another method of examination of the organs of the trunk from behind, sometimes ascribed to Letulle,¹ may be employed after examination of the brain, the skull and its cavities, the usual preliminary examination of the trunk cavities, and the organs and other important structures of the neck are all completed.

The structures of the neck are then cut across at the root of the neck by first lifting the right lung out of the thorax and inserting the point of the knife close to the spine on the right side and at about the level of the first thoracic vertebra and cutting forward and obliquely across the neck cephalad to the mouth of the thoracic duct so that all of the duct remains with the trunk organs. The diaphragm is then cut loose from close to the thorax on each side, the thorax organs cut loose from close to the thoracic vertebrae, and with all of the thorax organs held up at first vertically, they are gradually turned down over

¹ See Suggestions Regarding Postmortem Technic, E. R. LeCount, Jour. Amer. Med. Assoc., 1920, 75, 1611-1614.

and on to a pan placed across the thighs by continuing to dissect the abdominal organs in their turn away from the spine so far downward (caudad) that the back wall of the as yet uncut common iliac veins comes plainly into view (Fig. 22). In doing this special care is required to keep close to the spine where the crura of the diaphragm are attached so as to avoid opening the receptaculum chyli unwittingly.

This order of examining the trunk organs is then usually followed: the thoracic duct and its abdominal cysternæ, the azygos veins, inferior vena cava, hepatic, iliac, renal and ovarian or spermatic veins, supra-renal glands, perirenal fat, kidneys and ureters, periaortic and iliac lymph-glands, and the aorta and its branches below the diaphragm, as

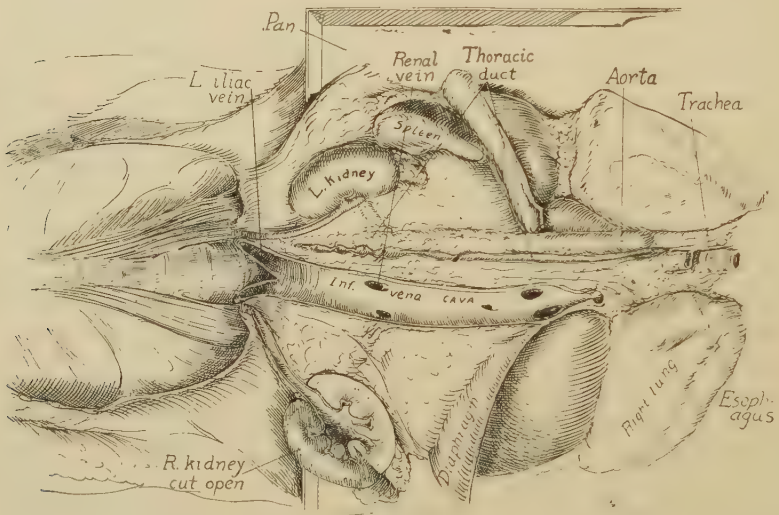


FIG. 22.—A graniteware or copper pan is laid across the thighs, and the organs of the trunk are dissected loose *en masse* and "turned down" on the pan with their posterior surfaces uppermost. In loosening them from the spine especial care is exercised to bare the front of the spine; and in this way the receptaculum chyli and thoracic duct are not injured. The last mentioned are best opened from below upward because of valves, and the examination from behind begins with this duct and periaortic and iliac lymph-glands, then the suprarenals, kidneys, ureters, inferior vena cava, renal, ovarian (spermatic), and hepatic veins, etc. In this figure, as well as in Figs. 23 and 24, that part of the trunk shown, as well as the organs, are represented as seen with the observer standing as usual on the right side of the table with the head to his left.

well as other structures, *e. g.*, celiac ganglions, vagus nerves, etc. Then the esophagus may be dissected loose from the tissues about it and turned caudad and, if desirable, the iliac arteries and aorta in a similar way dissected from their connections and turned cephalad (Fig. 23). Then the examination is continued, still from behind, of the thorax organs, beginning with the tracheobronchial lymph-glands, the trachea and main bronchi, pulmonary artery and veins, all of these (bronchi, arteries, and veins) being opened as far out into the lungs as desired. Following the opening and examination of the left auricle, which is done with the opening of the pulmonary veins, the median incision behind in the inferior vena cava is continued up through the back of the right

auricle into the superior vena cava, so that in its turn it is opened in its median wall behind.

Returning now to the abdomen, the fingers of one hand are slipped from the right side through the foramen epiploicum (of Winslow); and the inferior vena cava, still being uppermost, is cut across where it forms the back part of that ring. In this manner the ligamentum hepatoduodenale is exposed (Fig. 24) and the structures it contains are examined, beginning with the biliary and peripancreatic lymph-glands, the bile-ducts, the portal vein and its tributary veins, and the hepatic

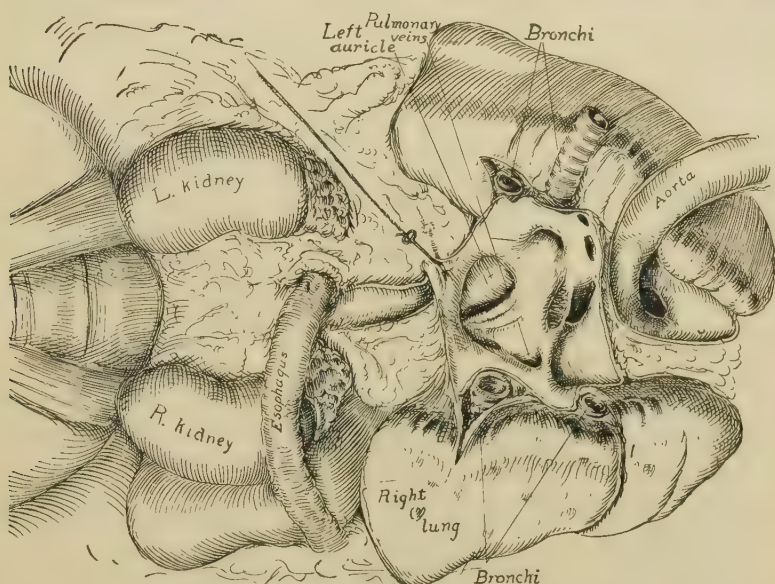


FIG. 23.—After the inferior vena cava and iliac veins (the latter not represented here) are opened, the aorta and iliac arteries slit lengthwise and reflected cephalad, the esophagus examined and laid caudad, and after the trachea, bronchi, and tracheobronchial lymph-glands are examined and the pulmonary artery and its branches far out into the lungs—all from behind; then the left auricle is opened as represented here, and the pulmonary veins are examined by opening them far out into the lungs. Then from the opened inferior cava a cut is made straight up through the right auricle in the midline into the superior cava, in its turn laid open in the middle behind, when the right auricle may be examined as was the left.

artery; then the gall-bladder and its duct connections, the pancreas, and the pancreatic ducts are examined.

The organs of the thorax and abdomen, still with nearly all of their mutual normal connections still intact, may then be returned to the cavity of the trunk and their examination continued from in front after the methods usually described in most accounts of postmortem technic, methods which include finally their removal for weighing and more particular examination and description as separate organs. These details are so generally known that no description of them is called for here.

Before the trunk organs are turned down over the thighs, the entire bowel mesentery and mesocolon, with the exception of the extra-

peritoneal parts of the duodenum and rectum, may be removed in one piece for separate examination if so desired; they may also with equal advantage be examined in the usual way after the trunk organs are returned to the body; at times their preliminary removal is an advantage; at other times, with extensive disease of the abdomen, such as tumors or thrombosis or embolism of mesenteric blood-vessels, it is advisable to allow them to retain their normal connections with other organs as long as possible.

Instructions usually given for the detailed examination of the pelvic organs from in front may be followed; or, before the trunk organs are turned down (Fig. 22) over the thighs, the pelvic organs can be loosened

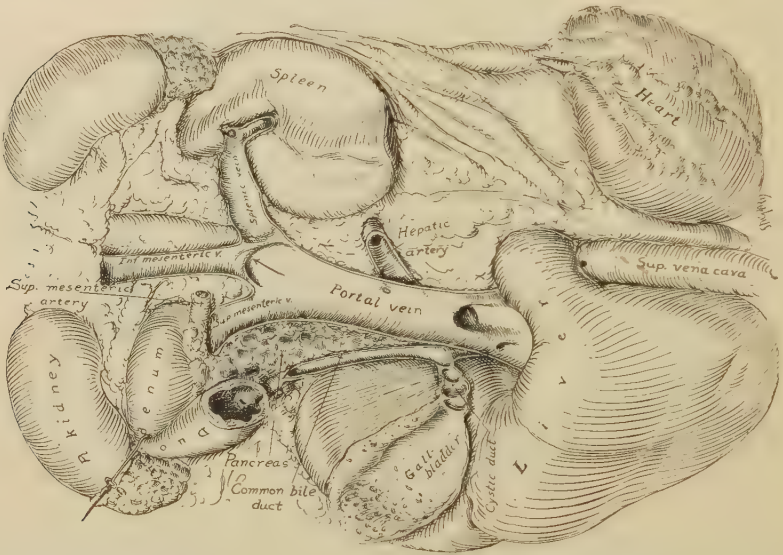


FIG. 24.—The distal end of the proximal segment of the duodenum, made by the cut across the duodenum, lies underneath the distal part of the common bile-duct represented as open. The heart has "rolled out" from its median position underneath. After the structures uppermost in this figure are examined, the arteries from the celiac axis are opened, then the pancreatic duct and stomach; or, if desired, the latter may be examined from in front after return of the organs of the trunk, all still with their normal attachments in the main intact, to the body cavities from which they were "turned down," over the thighs.

from the pelvis and with the perineum—and in the male with the testes and vasa deferentia—all, together with the trunk organs in one piece, may be lifted out of the trunk for examination. This has the advantage of allowing repair of the body to be begun by an assistant on an adjacent table when time is important.

ADVANTAGES OF THE PROCEDURE

It is assumed that the examination, as outlined, of the trunk and neck organs from behind is to be used, not to replace other methods, but rather to supplement them. There are many advantages to the procedure which will be apparent to all who are already accustomed to

making postmortem examinations and who perchance may not have already become as familiar with the approach from behind. These aids afforded are mainly connected with the greater ease of thorough examination of the large blood-vessels and their branches which lie so deeply in the trunk. The minute details of thrombosis of the iliac veins and ovarian veins, of embolism or thrombosis of the mesenteric or renal blood-vessels and of the portal vein, as well as the condition of the lymph-glands along the aorta and esophagus or about the trachea and bronchi, are all easily ascertained.

It also offers exceptional opportunity to learn the conditions with pulmonary embolism when the emboli are too small to occlude either the main pulmonary artery or its first divisions, but instead lodge in branches of the third or more distal subdivisions; moreover, with the organs turned over and out on the thighs, the front of the spine and inner surface of the cavity of the thorax are exposed quite thoroughly. The one great advantage is that the examination can be made as indicated and at the same time the normal connection of the trunk viscera to each other maintained until it is decided when and at what point their severance is desirable, and also that such cutting of them apart is not liable to lessen in any way the opportunity to understand and properly interpret either disease or its absence.

RESTORATION OF THE BODY

Upon the completion of the autopsy the body is to be placed in the most presentable condition attainable under the circumstances. This much is imperatively demanded from the humanitarian point of view. It is also to be borne in mind that any visible disfigurement of corpses over which public burial rites are to be performed would not tend to predispose the laity in favor of granting autopsies on patients that die in private or hospital practice. Hence the incisions should be so planned that their location is not conspicuous, and an effort should always be made to obliterate all evident traces of the autopsy, so that the fact that the body has been examined can be recognized only after more careful observation than is usually given dead bodies.

The body cavities should be sponged dry. Such organs as are not taken away should be returned to their respective cavities. The brain would better be placed in the thorax or abdomen, because it is difficult to force it back into the cranial cavity, which had best be filled with absorbent cotton or sawdust and shavings ("excelsior packing"), so as to prevent bloody fluid from oozing out through the incisions. Inasmuch as decomposition occurs more rapidly in bodies subject to post-mortem examination it is well to fill the chest and abdominal cavities also with absorbent material, in the summer-time especially. Foul odors may be prevented by dusting the interior of the cavities with some deodorizing and disinfecting powder. When the mouth has been forced open and the tongue removed with the organs of the neck, the lips may be united by a suture passed through the oral mucous membrane. The incisions at the pelvic outlet should be securely sutured

and the pelvis packed with absorbent material. In the place of bones that have been removed suitable pieces of wood can be inserted and, if necessary, wired in place.

It is advisable to secure the skull-cap in its normal position, so that the unsightly disfigurement which results from its sliding backward and from side to side may be avoided. Sutures through the divided temporal muscles and fascia on each side generally hold the calvaria nicely if passed well through the fascia; sutures can also be passed through drill-holes in the skull; double-ended tacks may also be used for this purpose. After securing the skull-cap the scalp is sutured with the glover's stitch, and the hair arranged so as to cover the incision.

All sutures used in closing cutaneous postmortem incisions are passed through the skin with a good-sized curved needle, and each margin of the incision is perforated in turn from within outward, so that the closure can be made quite tight, after the manner of the glover's stitch.

INORGANIC POISONS

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WHILE it is convenient to classify together the poisons derived from the mineral kingdom because they have a common origin in inorganic nature, a better reason is found in their similarities in chemical behavior and in the formation of their compounds. The mutual neutralization of acids and alkalis furnishes additional ground for this association. Another basis for so grouping them is found in the fact that almost all are irritants. Among them will be considered oxalic acid, which is not of mineral origin, but has a local irritant action and strongly acid chemical properties. The mineral poisons may be subdivided into *corrosives* and *irritants*, both of which produce a local organic mischief. Sometimes all are considered as irritants, and two classes are recognized: first, those which coagulate albuminous substances and thereby cause an eschar; and second, those which soften and dissolve the tissues, causing swelling and discoloration. In this classification the first group would include the corrosive acids, with oxalic and carbolic acids and such metallic irritants as corrosive mercuric chlorid. The primary local effect upon mucous membrane is a dry, cloudy, grayish-white condition, though the secondary effect of the acids is to cause yellow or brown discoloration. On the other hand, the members of the second group, composed of the corrosive alkalis, produce swelling and clearing up of the mucous membranes, with a dark color due to the imbibition of altered hematin by the submucous structures. When poisoning is due to carbolic acid or mercuric chlorid, the color of the blood in the affected parts shows through as a bright brick red.

CORROSIVE POISONS

The local action of this class of poisons is destructive. Applied to the skin, they have disorganizing effects analogous to those of a burn, and which, if extensive, may produce fatal consequences. Brought in contact with the mucous membranes, they have here a like destructive action; if swallowed, any part of the alimentary tract may be corroded, and the lining membrane of the larynx become the seat of acute inflammation with dangerous effusions.

The altered tissues are easily perforated and the contents of the stomach or intestines may escape into the peritoneal cavity. Death may ensue within a few hours from shock or the suffocation due to dropsical closure of the opening of the glottis.

Short of perforation, the corrosion may cause such wide-spread breaking down of the gastric glands as to annul their digesting power. An additional cause for slow starvation is found when the esophagus is narrowed, if not closed, by inflammatory exudations.

The **symptoms** come on at once and are well defined. In the mouth there is burning pain, with a strong taste characteristic of the class to which the poison belongs: sour if an acid, soapy if an alkali, and metallic if due to a metallic salt.

Immediately intense pain is felt in the throat and stomach, soon involving the whole abdomen. Vomiting and purging supervene, the discharges often showing blood, pure or altered by chemical action. There is thirst, with painful swallowing. The voice is faint and husky from the inflammation of the epiglottis and the larynx.

Stated broadly, the **postmortem appearances** are those of local softening or of hardening and contraction, with disintegration of tissue, either in circumscribed areas or largely distributed and surrounded by acutely inflamed tissues. A superficial erosion of the mucous membrane may be seen in one place, while in another the basement membrane may be involved, and in another a patch of the entire structure gives way, leaving openings into other parts. The differences in chemical action cause peculiar colorations, such as the yellow stain made by nitric acid and the brownish-black imbibition of altered hematin caused by sulphuric, hydrochloric, and oxalic acids, and also by the alkaline hydroxids. The corrosive poisons are subdivided into the *corrosive acids* and the *corrosive alkalis*.

CORROSIVE ACIDS

The mineral acids, sulphuric, nitric, and hydrochloric, are sour liquids which turn red the vegetable blue colors, such as litmus, and change the hue of dyed clothing mostly to red or yellow, while they injure the texture. When concentrated they rapidly destroy organic substances, and in the living body cause the most violent pain. They render the alkalis neutral and dissolve the common metals with effervescence. They are simple corrosives causing well-marked symptoms, due solely to their action on the part to which they are applied. In the United States the mineral acids are often taken by suicides, but as criminal poisons they do not figure in our records. In England and on the Continent they are frequently resorted to by the homicide.

The organic corrosive acid, oxalic, is a sour solid which may be given as an intensely acid solution, lacking the fierce dissolving power of the strong mineral acids and causing symptoms, some of which are local and common to other corrosives, but others also which are remote and specific in character, due to cerebrospinal involvement.

The antidotes owe their power to chemical neutralization, changing the fiery acids to harmless neutral salts.

Calcined magnesia, given freely suspended in water or milk, is a perfect antidote. When it cannot be had at once, as promptness is all important, prepared chalk, whiting used to polish silver, plaster scraped

from the wall, soapsuds, or largely diluted alkalis, such as sodium carbonate ("washing-soda"), sodium bicarbonate ("bread or baking soda," "saleratus"), sodium hydroxid ("concentrated lye"), or the corresponding compounds of potassium, should be given in milk or water. The soapsuds and alkalis are of no value against oxalic acid, as they form soluble alkaline oxalates which are absorbed and produce systemic poisoning.

It rarely happens that the antidote is given soon enough to prevent the energetic action of the poison, and even after thorough neutralization it would be best to give milk and very dilute alkaline solutions for some hours. As the tube of the stomach-pump or the siphon impinging upon the softened structures may do irreparable harm, it must not be used,¹ though later on the esophageal stricture may call for careful treatment by dilator and tubes.

SULPHURIC ACID

(Chemical formula, H_2SO_4 ; Synonym, *Oil of Vitriol*.)

There are few processes in the arts and manufactures that do not use at some stage the "oil of vitriol." It can be had at any chemists in common trade, and is used for cleansing metals as a household article. In countries where the law makes it difficult to purchase the arsenical or alkaloidal poisons, the ease with which sulphuric acid can be procured makes it a very common poison in use by the poorer classes for suicidal purposes, in spite of the pain that characterizes its action. It is rarely given in food for homicidal purposes, because it betrays the poisoner by the altered appearance of the charred food, by the stains on the clothing, lips, and tongue, by the fiery taste, and by the characteristic symptoms. It has been given to young children and even to adults in the form of medicine, taken, as disagreeable doses usually are, from a spoon back of the tongue, so as to avoid tasting.

Poisoning has occurred from the accidental substitution of it for oils, syrup, or glycerin. It has been poured into the ear, given by enema, and even injected into the vagina. From this poison there were 49 deaths in England and Wales for the five years from 1883 to 1887 inclusive. From journals ordinarily accessible there have been collected² 388 cases, of which 256 were fatal, 120 recovered, 53 were homicidal, 189 suicidal, and 99 accidental.

Local External Effects.—Malicious persons resort to it to disfigure the face or ruin the clothes of a rival by throwing a quantity of it at the hated person. Occasionally in chemical laboratories, while experimenting with it, flasks containing it will burst and the contents be dashed into the face of the experimenter. If it strikes the eye, blindness may result. In contact with the skin it causes great agony and a lasting scar. Instant action is necessary to prevent these serious effects. Water must be applied freely, the whole face immersed in a basin of it or held under a running tap, and the eyes opened under the

¹ Compare p. 30, under General Principles of Toxicology.

² Witthaus, Toxicology, 1911, p. 228.

water. A paste of sodium bicarbonate or a piece of soap will help to neutralize the residual acid at the burned points. The burn may be treated afterward with *linimentum calcis*. It is a common accident in the laboratory for the acid to fall upon the clothing. If not promptly touched with ammonia or some alkaline solution, the spot turns red and the fabric soon becomes rotten.

Properties.—Pure, strong sulphuric acid of a specific gravity not below 1.826 contains not less than 93 per cent. nor more than 95 per cent. of real acid (H_2SO_4), and is a colorless, heavy, oily liquid, not fuming, odorless, extremely sour, combining actively with water, and blackening or charring organic substances. The commercial “oil of vitriol” is not so pure, being colored light-brown by suspended carbonaceous matter and containing small amounts of dissolved metals, principally lead and arsenic. When added to water, heat is given out. If the proportion of the mixture is 3 of acid to 1 of water, the temperature will rise above 212°F . (100°C .). It has the property of abstracting water from the air, 100 grains under favorable conditions absorbing 120 grains of water in four days. This great affinity for water explains the charring action upon organic matter from which it abstracts the elements of water while dissolving all but the black carbon. When the concentrated acid is heated with zinc, copper, or other metals, the gas sulphur dioxide is liberated; if the acid be dilute, then if any action occurs, the gas evolved is hydrogen.

“Nordhausen acid” is a form manufactured in Bohemia and used largely in chemical manufactures. It is a dark-brown, heavy, oily, fuming liquid, with a specific gravity of 1.9. Its formula is $\text{H}_2\text{S}_2\text{O}_7$, and it is regarded by some as a solution of SO_3 in H_2SO_4 . Two weaker forms are used in medicine, the *dilute*, of 10 per cent., H_2SO_4 , and the *aromatic*, of 20 per cent., H_2SO_4 . It is applied externally as a powerful caustic in the shape of Ricord’s paste, made with powdered charcoal, and Michel’s paste, made with powdered asbestos.

Symptoms.—On the instant of contact with the mouth there is intense local pain, extending down the throat and gullet to the pit of the stomach, along the track of the acid. The tongue swells until it fills the mouth, and is covered with a white coating. Later it may be a corroded and shapeless mass.

The saliva flows profusely, but cannot be swallowed without pain, if at all, owing to the pharyngeal inflammation. Gasping and a hoarse voice denote that some of the acid has touched the larynx and caused spasmodic closure of the glottis.

The thirst is extreme, and is accompanied by persistent retching and vomiting. The ejected matter is very sour and slimy, often bloody, and loaded with portions of the mucous membrane of the gullet and stomach. The face has an agonized and anxious expression, the eyes look hollow, the nose is pinched and cold, the skin is clammy, the pulse is feeble, the breathing is difficult, and the extremities are convulsed. The case may end fatally in a few hours or after several days by asphyxia, stupor, or convulsions. When perforation of the stomach is

caused by rapid solution of its walls, the symptoms of fatal collapse rapidly develop and death is comparatively painless. When death is not so sudden and the inflammatory symptoms subside, the unfortunate one has a lingering death of starvation from stricture of the gullet or of the pylorus, and an incurable dyspepsia due to destruction of the coats of the stomach. Mendelssohn¹ reports the case of a woman of twenty-five years of age, who took, for suicidal purposes, a moderate amount of sulphuric acid and, surviving the immediate effects, had symptoms of gastric ulcer and enteric fever. After four weeks improvement began, but was arrested in the sixth week by attacks of vomiting. To relieve the pyloric stenosis resection was resorted to, but death followed in twelve hours. The gastric mucous membrane was almost wholly destroyed, the pylorus narrowed to the caliber of a small probe.

Fatal Dose.—The smallest fatal dose reported as given to an adult² is 60 grains (3.8 gm.). Death ensued in a child of one year after 20 drops.³ It is difficult to state the minimum limit of fatality, owing to the fact that much depends on the part touched by the acid and much on the amount of food present in the stomach. Even the smallest amount would be permanently injurious if it reached the gullet, causing narrowing of the food-channel. Few, if any, infants survive this poison, and of the adult cases, the mortality is two-thirds.⁴

Fatal Period.—In the infant quick inspiratory effort sometimes carries the poison into the larynx, and immediate death may ensue from spasmodic closure of the glottis.⁵ The shortest period recorded for the adult is one hour. Most cases die within twenty-four or thirty-six hours; some die from sequels after weeks, months, or years. In 160 fatal cases reported,⁶ 16 died in less than three hours; 60 in three to twenty-four hours; 35 in one to seven days; 18 in one to four weeks; 22 in one to three months; and 9 in more than three months.

Treatment.—Three objects are to be kept in view: First, prompt neutralization of the acid; second, weakening by dilution; third, relief of the asphyxia, which sometimes threatens life immediately. For neutralization magnesia and chalk are the best, but in an emergency soapsuds, whiting, or wall-plaster (an impure calcium carbonate) will serve the purpose. Weak alkaline solutions of sodium or potassium carbonate may be used with caution, as great distress, if not injury, to the weakened walls is possible from the stomach distention due to the liberation of large quantities of carbon dioxid gas. All the antidotes must be given suspended or dissolved in large quantities of water or milk. In the absence of a neutralizing antidote water alone must be used immediately and in large drafts, followed by raw eggs. Should symptoms of asphyxia appear as a result of laryngeal implication, then tracheotomy or intubation must be resorted to at once. Morphin

¹ Charité Annalen, 1887, xii, 183.

² Christison, R., *A Treatise on Poisons*, 1st. Am. ed., 1845, p. 131.

³ Taylor, A. S., *On Poisons*, 1875, p. 193.

⁴ Guy and Ferrier, *Principles of Forensic Medicine*, 7th ed., 1895, p. 475.

⁵ Thomson, *Lancet*, 1836-37, ii, 359.

⁶ Witthaus, *Toxicology*, 1911, p. 237.

may be given hypodermically to relieve pain, and nutritive enemata to support life. The sequels—perforation, collapse, contraction of the gullet, gastritis, and impaired digestion—must be treated by appropriate measures as the occasion arises.

Postmortem Appearances.—The *primary* pathologic changes found when death occurs within a few days are those of acute disorganization of the structures of the mouth, gullet, stomach, and neighboring parts. The lips and tongue are softened and eroded; the throat and gullet, whitish or gray in color, the first effect of the acid on mucous surfaces being to coat them with a white paint of altered secretion and membrane; the stomach is brown-red, due to imbibition of altered hematin or black from charring, its mucous lining loose in shreds or patches, the folds large and deep from swelling, sometimes softened so as to tear under gentle manipulation; the peritoneum may be blackened from perforation; the duodenum, red and thickened.

The *secondary* pathologic changes, seen when death follows after several weeks of chronic illness from some of the sequels, are ulceration of the gullet and contraction of its caliber from scars; the stomach is stripped of mucous membrane, partly or wholly red, its capacity much reduced by contraction, its walls thickened and adherent to neighboring parts.

Tests.—*Acid Test.*—The free acid, in common with other acids, reddens litmus, turns cochineal yellow, and decolorizes red phenolphthalein.

As proof of the presence of a *free mineral acid* litmus will not serve, as it is affected by acid salts and by the organic acids of digestion. Resort can be had to paper colored by certain anilin dyes which react to minute quantities of free mineral acids, but not in the same way to the organic acids nor to acid salts. A drop of the gastric contents containing a free mineral acid put on Congo-red paper leaves a dark-blue spot, while organic acids in large amount give a violet color; on tropæolin paper freshly prepared from an alcoholic solution (1 : 1000) it leaves a red-brown spot which changes to lilac when gently heated; on paper dipped in fresh solution of 1 gram of phloroglucin and 2 grams of vanillin in 30 grams of alcohol it turns red when heated in a capsule. A weak solution of methyl violet, distinctly violet in hue, is turned blue by adding a very weak mineral acid.

Barium Chlorid Test.—It is customary to test for sulphuric acid and the soluble sulphates by first acidulating with hydrochloric acid to prevent a precipitate being produced by the salts of certain other acids, such as carbonic, phosphoric, and oxalic, and then adding a solution of barium chlorid which throws down the white barium sulphate.

Charring Test.—When sulphuric acid is applied undiluted to white paper it darkens, and if gently heated chars, the paper; even if largely diluted, by heating the paper so as not to scorch it, the water evaporates and the acid will reach the charring-point. In some degree this property is shared by hydrochloric acid.

Veratrin Test.—A drop of the free acid will turn the alkaloid veratrin yellow, and finally an unchanging crimson. When the free acid is very dilute, a fragment of veratrin is dissolved in it by the aid of heat, and the colorless solution when evaporated to dryness in a water-bath leaves a residue having a crimson edge, which persists after many hours.

Detection.—In the majority of cases, when the acid gets upon the clothing by accidental dropping, by expectoration, or by vomiting, detection is comparatively easy. The strong acid will leave upon black cloth a damp spot which is at first red and afterward dirty brown and rotten. If the cloth is colored with indigo blue, there will be no red stain; if with logwood and madder, the stain will be yellow. The stain left by the dilute acid is also red, but the spot dries out and is not corroded. White linen or cotton will be blackened and eroded.

After many months or even years the acid may be detected in the spot by cutting out the piece, boiling it in 1 or 2 c.c. (20–40 drops) of distilled water, filtering, and testing with barium chlorid. A control experiment should be conducted simultaneously with a piece of the unstained cloth. Woolen textures often naturally contain sulphates, but if free sulphuric acid is present, the stain will turn blue litmus-paper red, will taste sour, and respond to the veratrin test. When some of the acid gets upon the lips, face, or hands, and is not instantly wiped or washed away, the burned spot does not blister but turns brown, whereas with nitric acid it would stain yellow, and with muriatic acid there would be no stain whatever. The corroded skin soon sloughs, and the wound fills up by granulation, leaving a permanent scar.

While it is true that the free acid is very rarely found in the stomach after death and “the chemical detection of a poisoning by nitric or sulphuric acid is, as a rule, impossible,”¹ yet in the majority of cases detection is rendered sure by a study of the surroundings, the characteristic pathologic effects, and the stains. Sometimes it happens that these are not conclusive, and appeal must be taken to a **quantitative analysis**. The gastric secretions and the food always contain some sulphates; others, such as magnesium sulphate, may have been given as a medicine. It is, therefore, necessary to estimate the total quantity of sulphates present and judge if the amount is greater than normal, and if it can be accounted for in any other way than by the administration of the acid itself. The mineral acids are usually separated from organic matter by digesting the mixture in distilled water for several hours. An acid reaction with litmus would point to free acid, and the degree of acidity could be determined by allowing the suspended matter to subside and then titrating a definite portion with decinormal sodium hydroxid, using phenolphthalein as an indicator. Some degree of acidity must be expected of the gastric contents from the presence of natural acids—hydrochloric, lactic, acetic, or butyric. The normal amount is so slight—not more than 0.3 per cent.—that any considerable showing of acid would be very significant.

¹ Buchner, *Lehrbuch der gerichtlichen Medicin*, 1867, p. 360.

To get the free sulphuric acid apart from free hydrochloric or butyric acids and separated from the sulphates and phosphates, the watery extract above referred to should be evaporated to dryness and treated with a mixture of equal parts of alcohol and ether. This mixture will separate the free sulphuric and phosphoric acids. By precipitation with acidified barium chlorid and weighing the dried precipitate of barium sulphate the amount of free sulphuric acid can be ascertained. The total quantity of the free acid and that combined as sulphates may be calculated by precipitation with barium chlorid from a definite fraction of the liquid containing a small amount of hydrochloric acid and heated to boiling. The liquid should be decanted, the precipitate washed, collected on a filter, dried, and weighed. One hundred parts of the barium sulphate precipitated represent 42 parts of absolute sulphuric acid (H_2SO_4) or 34.3 parts of sulphuric anhydrid (SO_3). By comparing the result with the small amount of sulphuric acid ordinarily present in a mixed meal (not more than 0.6 gram or 10 grains), the fact of excess can be made out.

According to Garnier,¹ the tissues rarely show free sulphuric acid, owing to its reaction with the phosphates. It forms sulphates with the bases and liberates the phosphoric acid. If the extract made with alcohol and ether, as stated above, when treated with ammonium molybdate, should yield a yellow precipitate, this would be an indication that free sulphuric acid had been present, unless it could be shown that free phosphoric acid had been given.

As the proportion of sulphates normally present in the *urine* varies with the individual, and in the same person changes from day to day, no forensic importance is to be attached to the analysis of the urine.

NITRIC ACID

(Chemical formula, HNO_3 ; Synonym, *Aqua Fortis*.)

Although widely used in the arts, this acid figures as a poison much less frequently than does sulphuric acid. History shows that most of the cases are suicidal, and when the intent is homicidal, the victim is either a child or an adult rendered unconscious by sleep or drunkenness. It would not be possible to give it in food or medicine without detection. According to the reports of the Registrar General of England from 1883 to 1887 inclusive, there were 29 cases of death from this cause in England and Wales. There were 6 cases of accidental death from it in New York City for the twenty-one years between 1870 and 1891 inclusive. In the medical journals² were found recorded 85 cases, of which 70 were fatal; 17 were homicidal, 43 suicidal, and 14 accidental. Metal workers use this acid for etching and for cleansing preparatory to gilding and lacquering. Of late years it has had a great extension of employment in various organic nitro-compounds, such as gun-cotton, celluloid, nitroglycerin, dynamite, and picric acid. Dyers, hatters, and chemists have need for it. In medicine the strong acid is

¹ *Annales d'Hyg.*, 1884, 3 S., xi, 227; 1887, 3 S., xvii, 148.

² Witthaus, *Toxicology*, 1911, p. 228.

a valued escharotic, but is not suited for internal administration, the dilute form, containing 10 per cent. of HNO_3 , being more eligible.

Properties.—The concentrated pure acid of the United States Pharmacopeia is a colorless, fuming, heavy liquid, with a specific gravity of 1.403, containing 68 per cent. of HNO_3 . On prolonged exposure to light and air the peroxid and other lower oxids of nitrogen are developed and impart a yellow color. It is then called nitroso-nitric or fuming acid. The *aqua fortis* of commerce is weaker, having a specific gravity of 1.25, is usually colored yellow, and fumes with the orange-colored vapor of mixed lower oxids. Most of the metals dissolve in it, but gold and platinum are exceptions. It corrodes organic matter by oxidation, not by carbonizing, as sulphuric acid does. Animal matter is turned a deep yellow, the color of picric acid. Albumin is coagulated by it, and if the acid is strong, the white coagulum turns the characteristic yellow. It gives promptly the acid reaction with litmus and other color indicators.

Symptoms.—The records of the comparatively few cases show no important difference from the symptoms produced by sulphuric acid and already described, with the exception of the color of the mouth and lips, which, with nitric acid, is intensely yellow, though at first the parts are blanched and white. There are intense pain, vomiting, thirst, and great depression. Eructations of gas are frequent and distressing, due to its direct development by the action of the acid on organic substances.

Fatal Dose.—Three drams by the mouth in an adult have destroyed life,¹ but a much smaller quantity would suffice to cause fatal suffocation from spasmodic closure if it were to enter the larynx, as it is likely to do in children.

Fatal Period.—The average duration of life is about twenty-four hours; the shortest time reported in the case of an adult² was an hour and three-quarters, while a case is recorded³ in an infant who died in a few minutes. In some cases death has been delayed for weeks, months, or years, the remote effects of the poison then proving fatal. In 39 fatal cases reported⁴ it is stated that 3 died in less than three hours, 12 in three to twenty-four hours, 9 in one to seven days, 5 in one to four weeks, 5 in one to three months, and 5 in more than three months.

Treatment.—The extraordinary energy and rapidity of action of nitric acid make it difficult to administer antidotes with sufficient promptness to be of much help. It is always advisable to use chalk, whiting, magnesia in milk, soapsuds, and eggs as antidotes, with the hope of neutralizing some free acid. The method is the same as for sulphuric acid and for the corrosive acids generally. In all there is instant local death of parts struck by the poison, rapidly followed by

¹ Warren, Records Boston Soc. for Med. Imp., 1853.

² A. S. Taylor, On Poisons, 1875, p. 209.

³ Ibid.

⁴ Witthaus, Toxicology, 1911, p. 237.

inflammation of surrounding viscera. Our antidotes cannot restore the tissues to health, nor can they diffuse into distant parts fast enough to be of much avail. The symptoms must be treated on general principles as they appear.

Postmortem Appearances.—All the parts to which the acid is applied present the various marks of erosion—in places hardening and thickening, in others ulceration and sloughing, general pulpiness, shreddy mucous surfaces denuded of membrane, and perforations of the gullet, the stomach, or the intestine. The most characteristic pathologic change is the permanent citron-yellow or orange-brown color of the tissues acted on.

Tests.—Even when very largely diluted—*i. e.*, to 0.2 per cent.—the acid reddens litmus. (See Tests for Free Mineral Acids, p. 128.)

Copper Test.—Poured upon slips of copper and gently heated, effervescence occurs and reddish-brown vapors arise that redden moist litmus-paper. If the amount of nitric acid is small, the color of the fumes may not be noticed, and a more delicate test is required. By holding in the vapors a piece of paper moistened with potassium iodid and starch paste, a blue color develops.

Brucin Test.—Upon a crystal of brucin a drop of nitric acid strikes a blood-red color; upon morphin an orange hue, with orange-colored fumes.

Ferrous Sulphate Test.—Upon a white porcelain surface put a few drops of the suspected liquid, a drop of sulphuric acid, and a crystal of ferrous sulphate; the crystal turns dark green, and finally brown. Even the combined acid in nitrates yields the same proof with any of the above tests, provided pure sulphuric acid is first used to free the nitric acid. If eggs have been given as an antidote, the nitric acid must be taken from the albumin by means of a solution of potassium carbonate; the resulting soluble nitrate can then be treated by equal parts of sulphuric acid and water before applying the above tests.

Detection.—On inspection the stains left on the clothing will be found dry and partaking of the same citron-yellow change found on the skin or other animal tissue touched by this acid. The yellow stain produced by tincture of iodine will be discharged by potassium hydroxid or by ammonia-water, but the nitric acid stain is indelible; ammonia and the alkalis only intensify it to an orange hue. If the piece of stained cloth is boiled in some distilled water, litmus-paper will reveal the acid reaction. When the acid liquid is neutralized with potassium carbonate, filtered, and evaporated to dryness, crystals of potassium nitrate form. When these crystals are dissolved in water and a drop of pure sulphuric acid is added, the nitric acid is set free and strikes a blood-red color with brucin, or yields ruddy fumes with copper turnings, or responds to any other test for nitric acid.

If the vomited matters are decidedly acid, the acidity should be measured by titration with decinormal solution of sodium hydroxid. The resulting sodium nitrate can then be tested by treating with sulphuric acid and applying any of the tests above mentioned.

As nitrates are not constituents of ordinary food or of the animal tissues, it is proof enough if these are found in any amount above a trace. It is not necessary to make a quantitative analysis. The vomited matters or the tissues should be extracted with boiling distilled water and potassium carbonate, and then filtered. Crystals of potassium nitrate are obtained on evaporation which respond to all the tests given above for nitrates.

Fumes of Nitric Acid.¹—The emanations of nitric acid are a mixture of nitric acid vapor with various lower oxids, all of them offensive and irritating to the air-passages. In the manufactures mentioned above as making use of this acid these vapors may do great harm if the processes are not carried on in closed vessels and the noxious fumes passed into milk of lime. The habitual breathing of air containing only a small amount frequently leads to severe chronic bronchitis with general impairment of health. In the annals of toxicology cases of acute poisoning are reported from chemists suddenly inhaling the fumes rising when a carboy of the acid has been accidentally broken. The symptoms are like those of capillary bronchitis. In the cellar of Jefferson Medical College is a supply-room in which carboys are kept. By accident a carboy of nitric acid had been left unstoppered, and after the summer vacation, the room having been closed for some weeks, a whitewasher worked in it for several hours until he was forced by illness to give up. He suffered from tightness of the chest, difficult breathing, dry cough, headache, nausea, and physical prostration, the symptoms not subsiding for a week or more.

In fatal cases there is found usually congestion of the larynx, trachea, and bronchial tubes, and sometimes edema of the lungs or effusion of blood. Although the effects appear to be mainly those of direct irritation, some cases show inflammatory changes in the lining of the right auricle. Acute cases should be treated by fresh air and inhalations of ether to relieve the sense of constriction.

HYDROCHLORIC ACID

(Chemical formula, HCl; Synonyms, *Muriatic Acid*, *Spirit of Salt*.)

In the ordinary acceptance by physicians, druggists, and manufacturers, this name is given to a liquid which, properly speaking, is a strong aqueous solution of the true acid, itself a gas imparting to the water its own chemical properties. By accident or for suicidal purposes it caused 90 deaths in the five years in England and Wales reported by the Registrar General. In New York City between 1870 and 1891 inclusive there were 6 cases of accidental death from this source. Out of 126 cases reported in medical journals,² it was found that 89 were fatal, 6 homicidal, 57 suicidal, and 40 accidental.

Properties.—Commercial hydrochloric or muriatic acid is a transparent, yellow, corrosive liquid. Its strength or percentage of pure acid gas is approximately the product of 200 and the decimals of the

¹ Consult also p. 343, Section on Gaseous Poisons.

² Witthaus Toxicology, 1911, p. 228.

specific gravity. Thus, a sample of a specific gravity of 1.15 should contain 30 per cent. HCl (200×0.15).

The chemically pure acid is colorless, the yellow color of the commercial article being due to a trace of iron from the apparatus used in its manufacture. A more important contaminant is arsenic, taken from the sulphuric acid used in generating it. The average amount of this impurity is 0.25 per cent. of arsenic trioxid. The pure acid liquid of the United States Pharmacopeia is sour, of pungent odor, and contains 450 volumes of gas dissolved in 1 volume of water, which increases more than one-third in bulk. It contains 31.9 per cent. by weight of the gas. The *dilute* acid of the Pharmacopeia contains 10 per cent. by weight of the anhydrous acid. On exposure to the air the strong acid gives off visible fumes due to the union and condensation of the invisible gas with the aqueous vapor of the air. The fumes have a pungent odor, an acid taste, are irrespirable, are one-fourth heavier than the air, and when allowed to blend with the fumes of ammonia, form dense white clouds of ammonium chlorid. The acid dissolves most of the metals, but not gold and platinum, and when heated with manganese dioxid, chlorin is set free. It is the natural acid of the gastric juice, and is used with pepsin as an aid to digestion. It is employed in chemical analysis as a group reagent, from its having the property of precipitating mercury (from mercurous salts), lead, and silver.

Symptoms.—This acid is very corrosive, like sulphuric and nitric acids already considered, but not so severe in its local action as either of the others. Owing to its volatility there is great liability of acute laryngeal inflammation from its irritating fumes, although the liquid itself may not enter the glottis. The lips, tongue, and throat are first white, but later become brown and rotten. There are instant pain in mouth, throat, and abdomen, difficult swallowing, husky voice, spasmodic breathing, retching and vomiting, feeble pulse, and general weakness, the mind remaining clear to the last. If the patient survive these acute symptoms, he remains subject to stricture of the gullet or pylorus, with loss of function of the stomach.

Fatal Dose.—As with the other acids, a few drops may prove fatal if they enter the larynx. By rapid swallowing and quick transmission to the stomach death may follow upon a fluidram dose.¹

Fatal Period.—From the acute effects death may ensue in fifteen hours or even in two hours, but, as a rule, the duration of life will be twenty-four hours. The secondary consequences are productive of a poor vitality for a variable period. One case has been reported of death from stricture of the pylorus after four months. In 64 fatal cases reported in medical literature 2 died in less than three hours, 27 in three to twenty-four hours, 12 in one to seven days, 9 in one to four weeks, 9 in one to three months, and 5 in more than three months.²

Treatment.—The remedial measures are the same as for sulphuric

¹ Johnson, Brit. Med. Jour., 1871, i, 221; see also Cleland, Med. Jour. Australia, 1920, i, 170.

² Witthaus, Toxicology, 1911, p. 237.

and nitric acids, the acid being neutralized by magnesia, chalk, plaster, soapsuds, or alkaline bicarbonates, given with milk, water, and raw eggs. The effects must be combated by general therapeutic rules.

Postmortem Appearances.—The pathologic changes found after death cannot be distinguished from those induced by sulphuric acid except by the local effects on lips and face.

Hydrochloric acid leaves no permanent stain or erosion externally, while sulphuric acid discolours and nitric acid turns yellow. Internally we find the signs of intense inflammation, with a shriveled and worm-eaten condition of the mucous membrane, which has a white or brownish color. The appearances due to sulphuric acid are the same except that the destruction of tissue is greater, but the yellow marks of nitric acid are always characteristic.

Tests.—The free acid gives the acid reaction to litmus. (See Tests for Free Mineral Acids, p. 128.) A glass stopper or rod wet with it and held near an open bottle of ammonia-water smokes with the white clouds of ammonium chlorid. Poured upon zinc it evolves hydrogen gas; if heated with manganese dioxid it yields greenish-yellow chlorin gas, which bleaches a piece of moist litmus-paper suspended in the vapor.

Silver Nitrate Test.—The chief test for chlorids serves equally for this acid—*i. e.*, silver nitrate, which gives a heavy, curdy, white precipitate of silver chlorid, soluble in ammonium hydroxid, but insoluble in nitric acid.

Detection.—Very little help is derived from a study of the stains on clothing. At first a reddish spot appears. On some black dyes the color is greenish, but owing to the volatility of the acid the spots are evanescent. They are not moist, charred, nor rotten as they are from sulphuric acid, nor are they yellow as from nitric acid. After a few days the moistened cloth will not affect litmus, but if boiled in water silver nitrate will show more chlorids in it than in the untouched cloth.

In the examination of the vomited matters we are liable to a fallacy from the natural presence of 0.2 per cent. of hydrochloric acid in the gastric juice, and from the chlorin in the alkaline chlorids of food.

If the material is strongly acid, sulphuric acid must first be tested for and excluded. Distillation will then collect the volatile hydrochloric acid, which can be estimated by titration with sodium hydroxid.

To determine both free acid and the combined chlorids, first make a filtered watery extract and divide it into two equal parts. One of these is neutralized by adding excess of sodium carbonate, which fixes the volatile free acid. Both are evaporated to dryness, the unneutralized portion losing all its free acid. Both residues are redissolved in water and are treated separately with acid solution of silver nitrate. If the neutralized portion shows more chlorids than the other, the difference equals the amount of free hydrochloric acid originally present in each portion. In this analysis 100 parts of silver chlorid precipitated represent about 80 parts of hydrochloric acid (specific gravity 1.15) or 25.43 parts of the anhydrous acid.

Nitromuriatic Acid.—By mixing 1 part of nitric and 3 parts of

hydrochloric acid the commercial *aqua regia* is prepared. This is an unstable liquid, evolving free chlorine and other gases, and eventually becoming much weaker than when first made. It dissolves all the metals, including gold and platinum, and oxidizes iodine, phosphorus, and sulphur. It coagulates albumin, turns it yellow, and finally dissolves it, as it does all vegetable and animal substances, with the production of ruddy fumes.

While the dilute acid is given internally as a medicine, the concentrated acid is an exceedingly corrosive poison, the symptoms and post-mortem appearances of which differ from those of nitric acid in degree only. The antidotes are the same as for the other mineral acids.

OXALIC ACID

(Chemical formula, $C_2H_2O_4 \cdot 2H_2O$; Synonym, *Acid of Sugar*.)

Oxalic acid and its salts are widely present in nature, being found in various plants, such as rhubarb (used for pies), nightshade, dock, sorrel (used for greens), and in animals also, occurring not infrequently as a constituent of the human urine. In the latter it is incidental to the gouty condition and some forms of dyspepsia, occurring as calcium oxalate in the form of a whitish deposit made up of microscopic crystals, octahedral or dumbbell shaped, and insoluble in warm water and in acetic acid.

It can be prepared from sugar by oxidation with nitric acid, and, therefore, is sometimes known in the arts as "acid of sugar." Its bleaching properties and solvent powers for metallic oxides make it useful to dyers and workers in leather, makers of straw hats and bonnets, and workers in marble and in brass. About the home it is used to remove ink-stains from linen. Druggists dispense it at low price, and consequently the would-be suicide not infrequently resorts to it. Its resemblance to Epsom salts leads to accidental poisoning, but the very sour taste is likely to betray the homicide, who rarely resorts to it except when it can be masked by some other sour beverage. In the five years from 1883 to 1887 inclusive there were registered in England and Wales 120 cases.¹ There were 14 accidental deaths from it in New York City in the twenty-one years from 1870 to 1891 inclusive.²

Of 242 cases³ reported in medical literature previous to 1910, 134 were suicides, of whom 55 were accidental. In the decade, 1871-80, in England and Wales, out of 1000 suicides by poison, 159 took oxalic acid.

Properties.—The crystals of oxalic acid are colorless, four-sided, prismatic, not deliquescent, and so closely resemble in appearance those of magnesium sulphate and zinc sulphate that it is often confounded with them. These crystals are very acid, soluble in about 10 parts of cold water and in $2\frac{1}{2}$ of cold alcohol, but very sparingly in ether. Heated on porcelain or platinum, it sublimes without residue.

¹ Registrar-General's Reports.

² Report of the New York City Board of Health.

³ Witthaus, *Toxicology*, 1911, p. 828.

It can be distinguished from the substances for which it is sometimes mistaken by the following ready tests, applicable in the household:

	Oxalic acid.	Magnesium sulphate.	Zinc sulphate
Taste.....	Sour.	Bitter, nauseous.	Bitter, metallic.
Reaction....	Very acid.	Neutral.	Slightly acid.
Heated.....	Sublimes.	Fixed.	Fixed.
Sodium carbonate..	No precipitate, but effervescence.	No effervescence, but a white precipitate.	No effervescence, but a white precipitate.
Ink.....	Bleaches.	No effect.	No effect.

Potassium Binoxalate (Chemical Formula, $\text{KHC}_2\text{O}_4 \cdot \text{H}_2\text{O}$).—This salt is usually dispensed by druggists to remove rust and ink-stains from linen, to bleach straw, and to polish metals, under the very deceptive name of “essential salts of lemon” and “salts of sorrel,” and sometimes without even the “grim heraldry of death” usually blazoned on labels for poisonous substances. It is sometimes dispensed as a white powder, although it crystallizes in colorless rhombic prisms; it has a decidedly acid reaction and sour taste, and is soluble in 40 parts of water. It is likely to be mistaken for cream of tartar, which is also a sour white solid. Almost equal to oxalic acid in the violence of its poisonous action, its symptoms, postmortem appearance, antidotes, and detection are practically the same.

Symptoms.—What is said of the toxic effects of oxalic acid is applicable also to potassium binoxalate. Like the acid, the soluble oxalates combine with the calcium in the tissues of the body and derange the equilibrium of health. While the symptoms vary considerably in different cases, they can be conveniently classified as, first, those due to the *local* erosive action on the mucous surfaces, and, second, those arising from the *remote* impression upon the nervous system—convulsive and narcotic. The symptoms produced by the local action of a strong solution and a large amount are very sour taste, thirst, pain and burning in mouth, throat, and stomach, difficult swallowing, vomiting of black or bloody substances, collapse. Occasionally pain is absent. Sometimes death may occur without vomiting.

“If,” says Christison,¹ “a person immediately after swallowing a solution of a crystalline salt which tasted purely and strongly acid is attacked with burning in the throat, then with burning in the stomach, vomiting, particularly of bloody matter, imperceptible pulse and excessive languor, and dies in half an hour, or still more in twenty, fifteen, or ten minutes, I do not know any fallacy which can interfere with the conclusion that oxalic acid was the cause of death. No parallel disease begins so abruptly and terminates so soon; and no other crystalline poison has the same effect.”

Hart² reports a case of oxalic acid poisoning in a boy aged fifteen years. Twelve minutes after the poison had been swallowed the patient was unconscious, his skin pallid and clammy, and his extremities cold. The radial pulse could not be felt. The pupils were fairly dilated.

¹ Christison, Treatise on Poisons, 1st Amer. ed., 1845, p. 179.

² Lancet, 1898, ii, 875.

The jaw was fixed in tetanic spasm, and froth exuded from between the teeth; $\frac{1}{10}$ grain of apomorphin was injected hypodermically; a stomach siphon-tube was introduced after the jaws had been forced apart, and 1 pint of warm water was placed in the stomach, but immediately expelled. Vomiting continued and consciousness returned. The boy was given $\frac{1}{2}$ ounce of powdered chalk, suspended in water, and this also was shortly ejected. Recovery proceeded under stimulation. The quantity of poison taken was upward of $2\frac{1}{2}$ drams.

If, owing to the smallness of the dose, death is not prompt, absorption of the poison ensues, and then the remote or *neurotic* symptoms appear. These are headache, cramps, convulsions, delirium, and coma. If the patient survives, there may be numbness and tingling, with loss of voice, lasting for weeks. When a small dose has been taken in dilute solution, the symptoms have not come on for hours, and then the nervous phenomena are more prominent.

Fatal Dose.—The least weight of the acid recorded as having fatal consequences is 1 dram (3.88 gm.).¹ Statistics show that the dose most likely to prove fatal is from $\frac{1}{2}$ to 1 ounce. Early vomiting and a measure of relief are caused by excessive doses. More than $\frac{1}{2}$ ounce (14.2 gm.), if retained, usually causes death, although recovery has occurred after a dose of 2 ounces.²

If efficient antidotes are instantly given there may be recovery from much larger doses, although the majority of cases prove fatal.

Fatal Period.—In 1 case death, supposed to be due to gastric hemorrhage, occurred without pain in *three minutes*.³ In other cases surviving the acute action on the alimentary tract death has occurred from coma after several days, 1 living until the twenty-third day. Out of 86 fatal cases, 78 lasted less than twenty-four hours; in 12 the victim was found dead, in 7 death occurred in less than ten minutes, in 19 in from ten to thirty minutes, in 11 in from one-half to one hour, in 3 in two hours, in 16 in from two to thirteen hours, in 5 in one and two days, in 10 in from two to five days, in 6 in from five to fourteen days.⁴

Treatment.—The chemical antidotes are finely divided chalk or calcined magnesia or its carbonate, suspended in a large quantity of water, and followed by free drafts of warm water to facilitate vomiting. As the toxic action is prompt, the antidote must be given at once. With a shovel or a kitchen knife the wall-plaster can be scraped off and used as an impure calcium carbonate.

Oxalic acid is chemically neutralized by the alkalis as well as by the alkaline earths (lime and magnesia), but the alkaline oxalates, being soluble and poisonous, are inadmissible, while the oxalates of calcium and magnesium are insoluble and innocuous. Emetics may be necessary, but the stomach-pump is likely to injure the eroded lining of the gullet and stomach.

¹ Barker, *Lancet*, 1885, ii, 1073.

² Tapson, *London Med. Gazette*, 1842, i, 491.

³ Ogilvie, *Lancet*, 1845, ii, 205.

⁴ Witthaus, *Toxicology*, 1911, p. 830.

Postmortem Appearances.—Colored stains upon the lips and face are absent, but the lips, tongue, throat, and gullet are usually white, and the lining membrane is loose, eroded in patches, and contracted into folds. Sometimes the stomach is black from extensive venous engorgement and contains blood or a brownish, grumous material; sometimes the membrane is pale and smooth, or detached in shreds; sometimes red, with the black veins strongly marked and corrugated. While deep erosions are not uncommon, it is rare to have complete solution of the walls of the stomach so as to cause the symptoms of perforation during life. Both peritonitis and pleuritis have been found as complications, and perforations of the stomach also, but these last in some cases have been supposed to be due to changes after death. The kidneys are congested and loaded with oxalates.

Tests.—A solution of oxalic acid or of potassium binoxalate reddens litmus-paper.

Calcium Test.—Either of them yields, with excess of calcium hydroxid, acetate, or sulphate, a white precipitate of calcium oxalate, insoluble in ammonia or acetic acid, but soluble in strong hydrochloric or nitric acid.

Silver Nitrate Test.—Either of them gives with silver nitrate a copious white precipitate of silver oxalate, soluble in ammonia and in nitric acid, while silver chlorid would be insoluble in the nitric acid. The silver oxalate, dried and heated on platinum, disperses with a slight explosion and a white smoke.

Lead Acetate Test.—With lead acetate a white precipitate of lead oxalate is formed which is soluble in nitric acid, but insoluble in acetic acid.

Potassium Permanganate Test.—Mixed with potassium permanganate and dilute sulphuric acid the oxalic acid is decomposed, and the permanganate, slowly losing its color, is converted into manganese sulphate.

Sublimation Test.—Heated on platinum foil, the acid crystals slowly sublime at as low a temperature as 100° C. (212° F.), and they are entirely and promptly dissipated at 150° C. (302° F.). The potassium binoxalate does not sublime, but changes to potassium carbonate, which effervesces when touched with an acid, and turns red litmus-paper blue.

Detection.—The symptoms of corrosive poisoning from an acid liquid which has left no colored spots upon the skin would be significant. A strong solution makes on black cloth a dark brown, uncorroded spot, which gives the oxalic acid reactions. The vomited matters should be searched for the leaves of sorrel or green material of the rhubarb pie; not that these are ever fatal, but so as to exclude the possibility of a complication in the analysis. In the vomited matters and gastric contents the acid will be partly free, partly combined as soluble oxalate, and partly combined as the insoluble calcium or magnesium oxalates. If it should be mostly free, the following method will serve:

1. Having made an extract with hot dilute hydrochloric acid and

filtered it, add lead acetate, which will throw down the lead oxalate along with various other lead compounds. This deposit should be suspended in water and hydrogen sulphid passed through it for two hours. The oxalic acid is set free in solution, the black lead sulphid being thrown down. After separation by a filter the filtrate should be tested with calcium acetate.

2. If the oxalic acid is in the combined state, the following is the better method: Digest the suspected matters with warm dilute hydrochloric acid until the mixture is quite fluid, filter, and to the filtrate add ammonium hydroxid until an alkaline reaction is reached. After standing the liquid is decanted and the deposit collected on a filter. This deposit is calcium oxalate. The filtrate mixed with the decanted fluid is treated with excess of calcium acetate and the precipitate separated on a filter. This second deposit represents the free acid in the original material. To determine the nature and amount of the first deposit, it should be washed with acetic acid on the filter and afterward put into a beaker and dissolved by cautiously adding strong hydrochloric acid and gently heating. Excess of ammonia will precipitate it completely if sufficient time is allowed. After decanting the clear fluid the deposit is washed by decantation, put into a tared dish, dried in a water-bath, and weighed. If this deposit is calcium oxalate, it will be white, and when a portion is heated on platinum, leave a gray ash of calcium carbonate. Another portion warmed in a test-tube with strong sulphuric acid evolves carbon dioxid gas, which can be identified by conducting it through a delivery tube into baryta-water. A third portion, suspended in water slightly acidulated with sulphuric acid, will discharge the purple color of potassium permanganate. This test can be applied by standard volumetric solutions and an estimate of quantity obtained.

If the poison has been taken as neutral sodium or potassium oxalate, the local symptoms and pathologic changes may not be at all characteristic. The effects come on after absorption and are mainly systemic. To make a complete examination the poison must be looked for outside the alimentary canal by separating it from the urine and the finely divided tissue of the kidney. The method would be the same as that for vomited matters containing the combined acid.

CORROSIVE ALKALIS

Under this heading will be considered the hydroxids or hydrates of potassium, sodium, and ammonium. It is well to note that their basic *carbonates* also are not only strongly alkaline in reaction, but in concentrated solution have a corrosive effect. The action of the corrosive alkalis is chemical or local, and limited to the part with which they come in contact. This corrosive power is due to their solvent action on albumin, their saponifying property when mixed with fatty matter, and their avidity for the water of the tissues. They cause rapid and deep destruction of the animal structures. The local symptoms are like those of the corrosive acids. The general symptoms are likewise those

of the shock of a violent lesion added to the immediate consequences of the lesion due to its locality. According to Falck,¹ out of 27 cases, 22 died (81.5 per cent.). Poisoning from them is most often accidental, though, according to the reports of Viennese hospitals, they are not infrequently taken for suicide.²

Reports of 167 cases of poisoning³ by the corrosive alkalis and carbonates showed that 22 were from impure sodium hydroxid, 3 from sodium carbonate, 44 from potassium hydroxid, 8 from potassium carbonate, 2 from a mixture of potassium hydroxid and carbonate, and 87 from "concentrated lye," etc.

Upon the salts of the alkaline metals neither hydrogen sulphid nor ammonium sulphid has any visible effect. Unlike the alkaline earths, they are not precipitated by ammonium carbonate.

POTASSIUM HYDROXID

(Chemical formula, KOH; Synonyms, *Potassium Hydrate*; *Caustic Potash*.)

Properties.—The pure substance is a grayish-white solid with an angular fracture. It imparts a soapy feeling when handled, has a soapy taste, and a strongly alkaline reaction to litmus. Heated, it melts to a colorless liquid; run into cylindric molds it makes *potassa fusa*, the ordinary form seen in the shops. It dissolves in half its weight of water, evolving heat; it is soluble also in alcohol and glycerin, but insoluble in ether. It deliquesces rapidly, and in the moist state freely takes up carbon dioxid gas to make potassium carbonate.

Pharmaceutic Preparations.—*Potassii hydroxidum*, or caustic potash, occurs in cylindric rods. *Liquor potassii hydroxidi*—solution of potash—is a colorless, acrid, alkaline, corrosive liquid with a specific gravity of 1.036, and containing about 5 per cent. of potassium hydroxid. *Potassa cum calce* (Vienna paste) is made of equal parts of potassa and quicklime. *Potassii carbonas impura* (pearlash), under the name of potashes, used for cleansing oil-lamps, occurs as a dark mass, deliquescent, strongly alkaline, and caustic. *Potassii carbonas pura* occurs as white crystals, deliquescent, alkaline, and caustic.

Symptoms.—Taken in strong solution, a large dose of caustic potash or the carbonate will cause a nauseous, soapy taste, accompanied by burning pain in mouth, throat, and stomach. Vomiting of alkaline bloody material soon follows, and later colicky pains and great abdominal tenderness with purging of shreds of epithelium, mucus, and blood. The lips and tongue swell and turn brown, swallowing is difficult, and the voice is hoarse. The pulse becomes feeble and rapid, the skin cold and damp, the breathing hurried and shallow. Surviving these symptoms, the patient may die after some days of starvation from stricture of the gullet.

Fatal Dose.—The ordinary fatal quantity is $\frac{1}{2}$ ounce, but 30 grains have proved sufficient.

¹ Falck, *Lehrb. d. prak. Toxikologie*, 1880.

² Hofmann, *Lehrb. d. gericht. Med.*, 9th ed., 1903, p. 681.

³ Witthaus, *Toxicology*, 1911, p. 315.

Fatal Period.—From the acute effects death may come in three hours; from the secondary effects, the final event may be delayed for weeks or even years. The average duration is about twenty-four hours.

Treatment.—The local action should be lessened by copious drafts of water alone or weakly acidulated. The chemical antidotes are weak acids and oils. The most convenient weak acid is vinegar, but diluted lemon-juice or orange-juice will serve. Milk, olive oil, melted butter, or lard would also neutralize the alkali, though not so promptly. The pain will call for morphin injections; collapse should be met by stimulants, and threatened starvation by nutritive enemata.

Postmortem Appearances.—The mouth, throat, and gullet are whitish and softened. The stomach and intestines are bright red or black from extravasated blood; the lining membrane disorganized and stripped in patches. The secondary pathologic changes seen when death closes the history of a chronic case are denudation of the lining membrane, ulceration, and points of stricture in gullet or pylorus.

Tests.—With excess of tartaric acid the potassium salts in strong solution give a colorless precipitate of potassium bitartrate, and with platinum chlorid a yellow precipitate insoluble in alcohol. To make these tests conclusive any ammonium salt must be removed by boiling with calcium hydroxid. To a colorless flame they impart a violet hue, and viewed by the spectroscope there is seen a characteristic combination of a dull-red band with a faint violet line.

Detection.—As alkalinity of the gastric contents has never been reported in any normal case, the mere fact that vomited matters or gastric contents have an alkaline reaction would be so exceptional as to be suspicious. After separating the soluble alkali from the undissolved matter by dialysis, the clear liquid should be titrated with decinormal sulphuric acid and tested for potassium. As the chlorid, sulphate, and phosphate of the metal are natural constituents of the food and of the body itself, more or less of these will be found always present. Hence, if the fluid is not alkaline, the process must include quantitative determinations of the different metals. If the analyst can obtain a sample of the substance taken or a piece of the clothing stained, his task is much simpler.

SODIUM HYDROXID

(Chemical formula, NaOH ; Synonyms, *Sodium Hydrate*; *Caustic Soda*.)

Under the name of "concentrated lye," an impure mixture of the hydroxid and the carbonate is largely used as a rapid cleanser in the laundry and in the making of soap. The author saw a case of a child of four years who, in playing about the laundry, out of curiosity ate some of the contents of a can containing "lye." The poison apparently did not reach the stomach, but corroded the throat and left a stricture of the gullet, which permitted swallowing of liquid food only. The patient slowly wasted away from starvation. There was no autopsy.

Properties.—The *hydroxid* occurs in gray-white masses or in molded sticks closely resembling potassium hydroxid. Like that, it is strongly

alkaline in reaction, soapy in taste, fuses by heat, dissolves freely in water with evolution of heat, is deliquescent, and in the moist state absorbs carbon dioxid from the air, forming the carbonate. This carbonate is not deliquescent like potassium carbonate, but efflorescent. When a can of caustic soda is opened, the solid will first liquefy, then absorb carbon dioxid, and finally solidify in a whitish powder.

Sodium carbonate, under the name of "sal soda" or "washing soda," is used as a domestic article to soften water and assist in cleansing. It occurs in rhombic octahedrons or in large angular masses which effloresce and crumble to powder. It is alkaline, acrid in taste, soluble, and caustic in every respect like the corresponding salt of potassium, only less severe.

Symptoms.—The symptoms are those of a corrosive poison, differing in degree only from those caused by potassium hydroxid and carbonate.

Fatal Dose.—About the same as for the potassium compounds.

Fatal Period.—The duration of life will depend on the dose and the lesions, and may be described as about the same as that given for the potassium compounds.

Treatment.—The antidotes are vinegar and lemon-juice to neutralize the alkali, and milk, oil, or butter to saponify it.

Postmortem Appearances.—The toxic effect is purely local. Although less active than the potassium compounds, the caustic forms of soda dissolve the albumin of the tissue, abstract the moisture, saponify the fatty material, and corrode deeply and widely.

Tests.—Unlike the potassium salts, the salts of sodium are not precipitated by tartaric acid nor by platinum chlorid. Its common salts are all soluble. With a fresh solution of *potassium antimoniate* they yield a white precipitate. To a colorless flame they impart an intense yellow color, which the spectroscope places as the bright D-line.

Detection.—The history of the case, inspection of inflamed spots on the face and hands, the strong soapy taste, and marked alkaline reaction of vomited matters will go far to prove a caustic alkali. The above given tests can be applied to determine the character, making allowance for the sodium chlorid always present in food and tissue. As commercial sodium hydroxid nearly always contains a small quantity of arsenic, a trace of the latter would strengthen the evidence in favor of the caustic alkali.

AMMONIUM HYDROXID

(Chemical formula, NH_4OH ; Synonyms, *Ammonium Hydrate*; *Ammonia-water*.)

Under the names of "hartshorn" and "anmonia," ammonium hydroxid is largely used in the household as a cleansing agent to remove paint, oil, and dirt generally from clothing. The following case which came under the observation of the author will show how easy it is to have accidental poisoning from it. An adult, unable to sleep, took from a closet a bottle containing a colorless fluid, which he supposed to be a solution of potassium bromid; the room being dimly lighted, he did not read the label, but took a tablespoonful of what proved to be ammonia-

water. He detected the poison as soon as it was tasted or smelt and before it was swallowed. For about a week his mouth and tongue were raw, swollen, and painful; he was unable to masticate or swallow solid food.

The liquefied ammonia gas (NH_3) is used in ice factories and refrigerators. Sometimes the receivers burst and the vapors fill the room, with deadly consequences to those who are exposed to them.¹ Sometimes, to arouse fainting persons, it is given too strong by inhalation. In the five years from 1883 to 1887 inclusive, 45 fatal cases were registered in England and Wales. Of 83 cases of poisoning by swallowing aqua ammoniæ or ammonium carbonate or "household ammonia" or aromatic spirits of ammonia, "Preston salts," it was found² that 49 were accidental, 27 suicidal, and 5 homicidal. Of 89 cases, 52 died and 37 recovered.

Properties.—Ammonia gas (NH_3) is a colorless gas having a pungent odor, irritating to the eyes and the mucous lining of the air-passages, turning moist red litmus-paper blue. Under a pressure of $6\frac{1}{2}$ atmospheres it is condensed to the liquid used in ice machines to create a freezing temperature by its evaporation. *Ammonium hydroxid* is a strong solution of the gas in water. Water will absorb 700 times its volume at ordinary temperatures and thereby acquire the alkalinity, the pungency, and the chemical properties of the gas itself.

Pharmaceutic Preparations.—*Aqua ammoniæ fortior* contains 28 per cent. by weight of ammonia gas, has a specific gravity of 0.897, and is a powerful corrosive. *Aqua ammoniæ* has $1\frac{1}{2}$ times more water, only 10 per cent. of ammonia gas, and a specific gravity of 0.958. *Spiritus ammoniæ* is a solution of the gas in alcohol, of the same strength as the aqua, and better adapted for internal use. When it has added to it the carbonate, with small quantities of oils of nutmeg, lemon, and lavender, the *aromatic spirits* is produced. *Ammonii carbonas* occurs as whitish angular masses, giving off the characteristic irritating and alkaline vapor of ammonia, and caustic in strong solution.

Symptoms.—The nature and gravity of the effects will depend greatly on the strength of the solution, and on whether or not the subject received a strong dose of the vapor by the lungs. The direct chemical action upon vital tissue is the same as that of potassium hydroxid, though less in degree—*i. e.*, the albumin is dissolved, the fatty matter saponified, and the water abstracted. The respiratory symptoms are a suffocative feeling due to spasm of the glottis, followed by a sense of pain and weight in the chest, with an irritative cough due to inflammation of the larynx and trachea.

The symptom due to the local caustic effect of the fluid is burning pain in mouth and throat, extending to the stomach if the poison went so far. There are salivation, vomiting, and difficulty in swallowing. As a result of a free absorption of the poison by the lungs and stomach cases display grave remote effects sometimes with great rapidity. The

¹ Fairbrother, St. Louis Medical and Surgical Journal, 1887, lii, 272.

² Witthaus, Toxicology, 1911, p. 328.

heart's action is sometimes arrested in a few minutes; sometimes there is immediate unconsciousness with coma, and death in a few minutes; sometimes there is unconscious delirium, soon ending in death.

A typical case is that reported by J. M. DaCosta¹: A man aged forty-six years took by mistake a large quantity of strong aqua ammoniæ, but swallowed only a small portion. In a short while the breathing was frequent and stertorous, the voice husky, the glottis, uvula, tonsils, lips, gums, and tongue all swollen. There were headache and delirium, enlarged cervical lymphatics, cough, with bloody expectoration. The urinary symptoms were remarkable, the secretion being diminished, but dense, alkaline, highly albuminous, showing separate blood-cells and many tube-casts, epithelial, hyaline, and granular. The serious symptoms soon subsided and convalescence set in after four days.

Fatal Dose.—A teaspoonful of the stronger aqua ammoniæ has in at least one instance proved fatal,² and 2 fluidrams have caused death in 2 or 3 other cases. Recovery, however, has sometimes followed much larger doses, such as a tablespoonful, and even upward of a fluidounce has been taken without fatal results.

Fatal Period.—By suffocation and syncope death has occurred in four minutes after inhalation of the gas. On the other hand, death may occur after many months as the result of the starvation due to stricture of the gullet or pylorus.

Treatment.—The antidotes are very weak vinegar, lemon-juice, oil, butter, and milk. The sequels are to be treated as they arise.

Postmortem Appearances.—These are not markedly different from the inflamed state of the alimentary tract as caused by the other caustic alkalis. When the vapor acts as an irritant upon the air-passages an inflamed state of the larynx and even of the bronchi may be found.

Tests.—Ammonia gas turns red litmus-paper blue, and makes a white smoke when mixed with the fumes of a rod wet with hydrochloric acid. All the salts are volatile when heated, and evolve the gas spontaneously or when heated with calcium hydroxid. Platinum chlorid yields a yellow precipitate like that given by potassium.

Detection.—Owing to the volatility of ammonia, its hydroxid and its carbonate, these soon escape from the body. During life, or soon after death, detection is easy by the characteristic odor. If the volatile preparation has been fixed by the antidote, the vapor can be developed by heating the material with lime. This vapor will be alkaline and forms white fumes with hydrochloric acid.

If the organic material to be examined is putrid, allowance must be made for the ammonia produced by putrefaction. This is never enough to develop the dense white fumes of ammonium chlorid from a rod wet with hydrochloric acid. The amount may be estimated by distillation, neutralizing the distillate with hydrochloric acid, evaporating nearly to dryness, and precipitating the double chlorid of ammonium and platinum by adding excess of alcoholic solution of platinum chlorid.

¹ Boston Medical and Surgical Journal, 1891, cxxv, 677.

² Stevenson, Guy's Hospital Reports, 1871, 3 S., xvii, 225.

After filtration, the precipitate is washed with alcohol, dried, and weighed; 100 parts represent 8.6 parts of ammonia (NH_3).

IRRITANT POISONS

In the class of irritants are placed a large number of poisons that figure prominently in the bills of mortality. Some of them are of animal and some of vegetable origin, but the present study is limited to those derived from the mineral kingdom. They cause pain in the throat, gullet, and stomach, great thirst, nausea and vomiting, abdominal tenderness, purging and straining, with bloody stools, scanty, and often albuminous, urine. After death the alimentary tract shows an inflamed condition not very characteristic except when it involves the entire length from mouth to rectum, an extent never found in the specific inflammatory affections of the stomach and bowels, such as cholera morbus and acute gastric or intestinal catarrh. There are redness and swelling of the mucous glands, dark patches of infiltrated blood, softening, and as a secondary result of the inflammation ulceration and perforation (see Plate 2). With those minerals that add remote effects to the local ones just given there are symptoms and pathologic changes referable to the specific organs affected, as the heart, liver, and kidney.

PHOSPHORUS

(Chemical symbol, P.)

This element is a constituent of the tissues and fluids of the human body, occurring largely in the bones as calcium phosphate and in the nervous centers as a compound with fat and albumin. Ever since it was first used to tip lucifer matches its poisonous properties have been known; indeed, on the Continent of Europe it has been the favorite rat poison. While the other active poisons are guarded by law from general distribution, this one is easily obtained as the heads of matches and as "rat-paste," which contains from 1 to 4 per cent. of phosphorus mixed with oil, flour, sugar, and coloring-matter.¹ It is rarely used by homicides, but frequently by suicides, and sometimes children ignorantly eat the paste or suck the heads of matches. In the five years from 1883 to 1887 inclusive there were registered in England 71 deaths from poisoning by phosphorus and matches.² More than half the cases were in children. Of the adults, nearly all were suicidal, a few only being accidental and none criminal. In spite of the garlicky taste and smell, it could be given in coffee, the more easily if at the same meal onions or garlic had been eaten. Out of 802 cases reported,³ in only 26 was the substance anything but match-heads or vermin-poison: 123 were homicidal, 388 suicidal, 88 accidental, 67 taken to cause abortion, 1 by experiment, 2 by quacks. Of the 123 homicidal cases, only 3 were in

¹ Coster's Rat and Roach Exterminator contains 2.13 per cent. of phosphorus, and though the buyer is assured by the label that it is "not poisonous," 2 fatal cases have been reported from taking it. Parson and Co.'s Vermin Exterminator has 0.4 per cent. of free phosphorus.

² Repts. of Registrar-general.

³ Witthaus, Toxicology, 1911, pp. 634-637.

the United States; of the 388 suicidal, 249 were in Germany and Austria and 5 in the United States; of the suicidal cases, 229 were women, many of whom probably took it to produce abortion. Stacy¹ has reported the death of his own child of fifteen months following the eating of unburned portions of certain fireworks containing phosphorus. The course was typical, death occurring on the fourth day.

Properties.—The *ordinary crystalline* or *waxy* form usually occurs in translucent cylinders which cut like wax, and when kept under water turn yellow and become coated with a thin white crust. As it oxidizes in the air it should be kept under water that has been well boiled. It takes fire at 122° F. (50° C.), a temperature easily reached by friction between the fingers, hence the caution to handle it with forceps. If it should take fire in the hand, it will burn severely, and at the same time more or less of the poison will be absorbed. The poison in the burn should be made inert by a lotion of chlorinated soda or a paste of chlorinated lime.

It has the odor and taste of garlic, is very sparingly soluble in water, slightly soluble in alcohol and glycerin, but freely so in carbon bisulphid, almond oil, and ether. Under water at 111° F. (44.5° C.) it melts to an oily fluid, which can be run into cylindric molds. Exposed to the air, white fumes of its lower oxid are evolved, and in the dark emit a feeble light.

Red phosphorus is an allotropic form, made by heating the ordinary form in a closed vessel without air for thirty-six hours. It is a reddish-brown powder which does not oxidize in air, need not be kept under water, and requires a much higher temperature to inflame it than does the waxy form. The pure red phosphorus is not poisonous, but the commercial article sometimes contains as much as 0.6 per cent. of the waxy, poisonous form.

The *lucifer matches* commonly sold are tipped with waxy or poisonous phosphorus mixed with potassium chlorate, sand, and glue, but the "*safety*" match is tipped with potassium chlorate and antimony sulphid without phosphorus. In order to light the "*safety*" match it must be rubbed upon the side of the containing box, which is covered with a thin coat of red or non-poisonous phosphorus, mixed with sizing.

Pharmaceutic Preparations.—Phosphorus is usually given in a pill mass with althæa or acacia or some other excipient and coated with sugar or gelatin to prevent oxidation. The presence of the free phosphorus can be shown by cutting the pill open and exposing the mass to gentle heat in the dark. It should "phosphoresce"—i. e., emit light. *Oleum phosphoratum* is a solution in almond oil of 1 per cent. strength. *Spiritus phosphori* is a solution in absolute alcohol of about 0.1 per cent. strength. An *ethereal* solution is also used.

Phosphin (Chemical formula, PH_3).—*Phosphorus terhydrid* or *phosphuretted hydrogen* when inhaled is a very poisonous gas, reducing the oxyhemoglobin of the blood. It can be made by boiling phosphorus

¹ Jour. Amer. Med. Assoc., 1921, 77, 1514. See also Corwin, New York State Jour. Med., 1922, 22, 475.

with strong potash or soda lye, or by generating hydrogen in the presence of phosphorus or its lower oxids. It is colorless, sparingly soluble, and, as ordinarily made, inflames spontaneously on contact with the air. When evolved with hydrogen it burns with a greenish flame, but if dry and insufficiently supplied with air, the flame is white. When passed through a solution of silver nitrate, the silver is deposited as metal, leaving nitric and phosphoric acids in solution; by adding excess of molybdic acid the phosphoric acid can be detected.

Symptoms.—If the phosphorus be taken in lumps, the effect is not proportionate to the weight. To be fully effectual it must be dissolved or finely divided, as it is in the rat-pastes and pill masses.

The cases of poisoning are often referred by their symptoms to one of the three classes established by the researches of Tardieu¹—a common form, showing symptoms of local irritation and jaundice; a hemorrhagic form like scurvy, in which jaundice and effusions of blood occur; and a nervous form, in which jaundice is accompanied by creeping sensations, cramps, drowsiness, delirium, and convulsions.

Nearly 90 per cent. of the cases suffer from *acute irritation* followed by *jaundice* and *profound blood changes*. Complaint is made that the substance taken had the taste and odor of garlic. Sometimes violent pain in the throat, gullet, and stomach is experienced immediately, accompanied by vomiting and purging. The breath is phosphorescent, and the ejected matters may be bloody, garlicky in odor, and emit light when stirred in a shallow dish. In a large number of cases there is an interval of several hours between the taking of the poison and any symptom whatever.

Death from collapse may come at this early stage, but usually the irritation abates and *jaundice* sets in after a period of comparative comfort. This quiet interval usually lasts from two to three days, but it may be only one day in length or be prolonged for several weeks. The jaundice portends more or less profound *blood changes*. In addition to the general effects wrought by the biliary matters in the circulation, there will be the toxic symptoms, caused by the presence of phosphorus derivatives. Given in detail, there will be yellowness of skin and conjunctiva and tenderness over the liver, with an increased area of hepatic dulness. Headache, insomnia, and itching eruptions of the skin are common. The urine is saffron-yellow or olive-green in color from the presence of bile-pigments, scanty, albuminous, bloody, containing tube-casts and occasionally leucin and tyrosin. Extreme weakness culminating in *heart failure* is a characteristic due to the degenerations of the muscular tissue, including the heart. These stormy signs soon culminate in delirium, convulsions, coma, syncope, and death.

In a certain proportion of cases, not necessarily fatal, the toxic effects on the blood and its vessels are made conspicuous by the *hemorrhages* which accompany the jaundice. Blood may be effused under the skin in spots or pass out by one or more of the mucous channels. Hemorrhage has occurred from the nose, mouth, bowels, kidneys, and bladder

¹ Tardieu, *Etude Médico-légale*, etc., 1867.

all at once. Women will have uterine hemorrhage, and if pregnant, will abort, with alarming flooding. Anemia and exhaustion reach an extreme stage, and delirium ending in death may supervene after months have elapsed since the administration of the poison. Even when the direct influence of the poison has passed away and life is no longer threatened, there may be persistent debility and local palsies.

The rarest form of acute poisoning is that in which the *nervous phenomena* are the most conspicuous. This form is likely to occur when the case is one of inhalation of fatal quantities of phosphorus vapor. In the preparation of "rat-paste" or in the making of matches the materials may be accidentally heated so as suddenly to evolve large quantities of phosphorus vapor. The effects are fainting attacks, succeeded by profound prostration with extreme muscular weakness.

Emphasis must be laid upon the variety of the symptoms, permitting of many different clinical pictures, and also upon their insidious development. There can be but little doubt that at one time many cases were incorrectly diagnosed as acute yellow atrophy of the liver. This is not surprising, as the history of the case after the liver symptoms appear is the same as in acute yellow atrophy, even to the contraction of the organ itself. In a very small proportion of cases surviving a week jaundice does not occur. Casper reports a case that lived for twelve hours, the only marked symptoms being one act of vomiting and a garlicky odor of the breath, which was luminous in the dark.

West¹ reported a case of unusual delay in the supervention of fatal jaundice. A woman of fifty-two took phosphorus rat-poison. Within fifteen minutes she had burning in the mouth and abdominal pain. Emetics and turpentine were given. In twelve days she was considered well. Four weeks later jaundice set in, with great depression, black vomit, and pains in the head, back, and legs. In six days she died. The autopsy revealed a large, firm, pale yellow, and fatty liver.

Fatal Dose.—In the treatment of nervous diseases the usual dose is $\frac{1}{50}$ grain thrice daily, but some persons can bear gradual increase to as much as $\frac{1}{4}$ grain. It would be risky to begin with these maximum quantities, as the subjects of nervous diseases are usually very susceptible. A lunatic under the observation of Lobel died from the effects of 7.5 mg. (0.116 gr.).

A healthy adult would have his life put in jeopardy from 1 grain taken in a finely divided form, such as the pill, paste, or the match-head. A child is reported to have died from sucking the heads of two matches, containing about $\frac{1}{50}$ grain of phosphorus. On the other hand, there has been recovery after ten packages of matches have been sucked.²

Fatal Period.—Death has occurred in less than one hour, but the duration of life is very diverse in different cases. Some die in four

¹ Lancet, 1893, i, 245.

² Singer, Prager med. Wochenschr., 1883, viii, 509.

hours; three-fourths of the cases die within a week; some cases become chronic, the patient dying a lingering death after many months.

Treatment.—In considering the best remedial procedures it must be noted that great differences have been observed in the time of onset of the symptoms. In the majority they commence after an interval of from two to six hours; in a few they are described as immediate; in four-fifths they come on within six hours. In every case presenting a history of a poisonous dose the treatment should be instituted at once, instead of waiting for the symptoms to appear. There is need for instant evacuation by the stomach-tube and washing out of the stomach with a solution of *potassium permanganate* of the strength of 0.5 to 1 per cent. (about 4 gr. to the fluidounce), leaving about a pint in the stomach. This antidote, introduced by Antal, of Budapest, has a chemical reaction with the phosphorus, by which the latter is said to be changed to harmless compounds. Potassium permanganate oxidizes the phosphorus, forming phosphoric acid and phosphates, itself changing to manganese dioxid. In the absence of a stomach-tube the antidote should be given—4 grains in an ounce of water, frequently repeated. The permanganate is in part reduced by the organic substances of the food, and hence the necessity of giving it in excess, although in a dilute solution to avoid gastric irritation. Quite recently Fr. Lanz has analyzed the results of treating 39 cases with potassium permanganate. He considers that these cases do not speak in favor of potassium permanganate as an antidote.

Copper sulphate is often recommended as an antidote. When its solution is mixed with phosphorus in a test-tube the phosphorus is seen to change instantly to black copper phosphid, which is not injurious. There is one drawback to its use. In the quantities recommended and needed for full antidotal effect (3 grains frequently repeated) the copper salt is a decided irritant and is likely to aggravate the gastro-enteritis or set up a violent one of its own unless in very dilute solution.

Another antidote honored by text-book commendation is turpentine. It is said to combine with the phosphorus to produce phosphoroterebinthinic acid, a non-poisonous solid. To be efficient the article must be an old acid sample, and some enjoin that the French article alone is of any value. As old French turpentine is not the kind kept officially by druggists, it is practically out of the question.

Good results have been obtained by washing out the stomach with warm water until the smell of phosphorus disappears, continuing the administration of magnesium oxid suspended in water. This may be followed by solution of copper sulphate or emulsion of turpentine, and later by sodium bicarbonate. Evacuation of the bowels should be secured by the use of turpentine in doses of $\frac{1}{2}$ dram given in an emulsion with mucilage every half-hour. As the phosphorus tends to adhere to the mucous folds of the small intestine, it is advisable to maintain purgation by giving the turpentine for several days. Although most writers warn against the use of oils, Atkinson¹ advises the use of liquid petro-

¹ Jour. Lab. and Clin. Med., 1921, 7, 148.

latum as an unabsorbable solvent for the free phosphorus, his theory being based upon animal experiments as well as upon the treatment of an actual case of phosphorus poisoning.

Postmortem Appearances.—The general toxic effect of phosphorus is to induce a wide-spread degeneration of glandular and muscular tissue. This degeneration consists in the formation of fat in place of the true cellular tissue. It is presumable that those cases of death in which no change has been found postmortem would have yielded a different report if the microscope had been used to aid the naked eye. The *stomach* may be free from signs of disease, although, as a rule, there will be a fatty degeneration of the epithelial cells, with thickening of the mucous membrane, due to enlargement of the glands and an occlusion by large granular cells. This condition obtains in the intestines and is often associated with hemorrhagic foci and minute inflamed areas. These appearances are found also in diseases due to septic conditions of the blood.

Even at an early period the *liver* is the seat of fatty degeneration. If seen early, it may be enlarged, yellow, deficient in blood, and present a mottled section. Under the microscope the hepatic cells are found to lack definition and to be granular or filled with large fat-globules. When death follows a chronic history, the liver may be found atrophied and the changes more profound.

The capsule of the *kidney* is easily stripped. Under it are found hemorrhagic patches. The organ itself is enlarged, and its epithelial cells and vascular walls are infiltrated with granular fat.

The transverse stripes of the muscular fibers of the *heart* are replaced by fat, a form of change seen in the muscular system generally. If the case has been one of the hemorrhagic type, there will be extravasations of blood in the tubules of the kidney, in the endocardium, the peritoneum, the pleura, the mediastinum, and many other places.

Hill¹ has reported a case having points of interest. A girl of fifteen smeared rat-poison on her hands and face for a luminous effect at a "dark séance." She had headache, faintness, bloody vomit, jaundice, constipation, offensive breath, weak pulse, tender abdomen, diminished liver dulness, and coma, dying on the eighth day. At the autopsy the heart was friable and yellow; the gastric rugæ were black, swollen, and softened; the intestines were filled with altered blood, and the mucous membrane was altered like that of the stomach; the liver weighed but 45½ ounces, showed a chrome-yellow color externally and internally, was soft, friable, and greasy, and the section displayed lobules marked out by fatty and congested areas. The kidneys showed red pyramids and very pale cortex. The odor of phosphorus was detected in the brain, but there was no luminosity of the organs.

Distribution in the Tissues.—Lemkes² in a study of the cadavers of poisoned animals found unoxidized phosphorus in the liver, skin, blood, and urine, but never in the brain. It was present as late as ninety-

¹ Lancet, 1890, i, 398.

² Pharm. Weekblad, 1916, 53, 1496.

seven days after death. Negative results only were obtained by tests for volatile phosphorus compounds formed during decomposition of albuminous substances.

Chronic Poisoning.—Makers of phosphorus or weakly individuals working in match factories which make use of white or yellow phosphorus or even its much less poisonous compound—*phosphorus sulphid*, P_4S_3 —whose occupation requires that they must inhale phosphorus fumes daily, become the subject of "lucifer disease" or "phosphorus necrosis." After several weeks or months obstinate toothache is felt, and when the tooth is extracted the gum does not heal, but retracts, leaving a suppurating bony surface. Pieces of bone come away, and the disease process in the marrow and in the periosteum spreads to new areas, other teeth and their sockets become involved, and greater portions of bone necrosed. Accompanying the local mischief, partly caused by it and also aggravating it, is a general disturbance of health characterized by anemia, pallor, weakness, hectic fever, diarrhea, septicemia, purpura, sometimes ending in death by exhaustion. These symptoms may be prevented by dental inspection of workmen and filling of all carious spots on the teeth, by the circulation of fresh air, by the frequent and systematic use of mouth-washes of sodium bicarbonate, and by the prompt exclusion of any one showing significant symptoms. A milder form of chronic poisoning than the necrosis of the jaw is often encountered, the symptoms of which are anemia, slight jaundice, cachexia, albuminuria, and, later on, chronic bronchitis, enteritis, and fragility of the bones.

The use of "safety matches" and varieties substituting the red or non-poisonous form is spreading, and with better hygienic measures bids fair to remove "phossy jaw" from the bills of mortality. The manufacture and sale of white or ordinary phosphorus matches was stopped in Germany since 1907, and in Great Britain and Ireland is prohibited by a law which came into force January 1, 1910¹ (8 Edw. 7, Ch. 42). In the United States a Federal act approved April 9, 1912 provides for a tax on white phosphorus matches, which is practically prohibitory.² Many states require notification of cases of phosphorus poisoning, while some have legislated against "Parlor Matches" specifically (1912-13). Phosphorus affected only a small proportion of workmen exposed in factories in 1921, as white phosphorus is now little used in American industry.³ Stockman⁴ found the bacillus of tuberculosis in the pus formed in the carious jaws, and advocates early operations to remove the original foci at the root of the tooth. He takes the position that in a large proportion of cases the phosphorus, by eroding the bone, makes it susceptible to tuberculous infection, which manifests itself later asiliary tuberculosis, meningitis, or phthisis, pulmonary and abdominal.

¹ Drug. Circ., 1911, v, 55, p. 76.

² Bull. No. 56, U. S. Pub. Health Service.

³ Hamilton, Chem. Trade Jour., 1919, 65, 365.

⁴ Brit. Med. Jour., 1899, i, 9.

Tests.—The tests for phosphorus are its peculiar odor, its luminous appearance in the dark, and the power of reduction possessed by it over silver nitrate.

Detection.—The garlicky odor is suspicious, but may be masked by articles of food having a similar odor, such as onions. If the room be darkened, the breath will shine faintly and phosphorescent spots will be seen upon the lips or clothing. The vomited matters or the urine if put into a test-tube, acidulated with sulphuric acid, and gently heated, will evolve luminous fumes. A piece of white paper molded as a lid to the tube (Fig. 25) should be wet with a drop of a strong solution of silver nitrate. The phosphorus vapor will cause the metallic silver to be reduced as a black spot on the paper. To prove that this is not produced by hydrogen sulphid, the same test should be repeated after adding some lead acetate to fix the hydrogen



FIG. 25.—Apparatus for testing phosphorus vapor with silver nitrate.

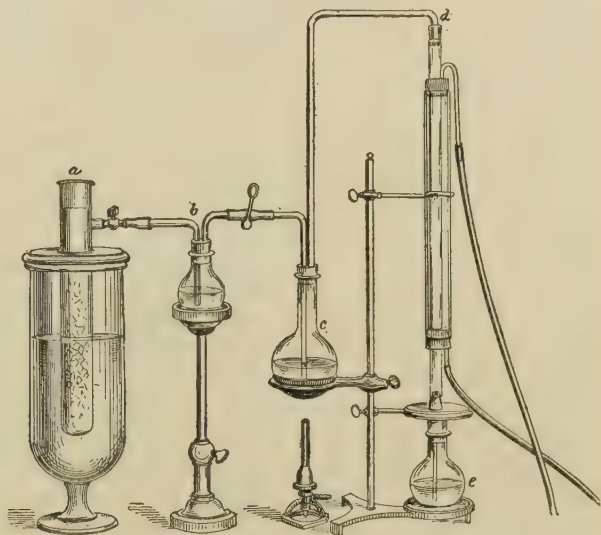


FIG. 26.—Mitscherlich's test for phosphorus: *a*, Generator for CO₂; *b*, wash bottle; *c*, suspected material; *d*, condenser; *e*, receiver for distillate.

sulphid in the liquid, or a plug of absorbent cotton wet with lead acetate may be put in the neck of the tube. When the phosphorus is present in minute quantities it will not be evident by this test unless performed by the careful method of Mitscherlich.

Mitscherlich's Test.—The suspected material is put into a flask (Fig. 26, *c*) and acidulated with sulphuric acid to prevent the escape of ammoniacal vapors. When heated gradually by the sand-bath the phosphorus vaporizes, and is conducted by a long delivery tube to a glass Liebig's condenser, *d*, kept cold by water circulating around the inner tube. The room being totally dark, flashes of light and shining clouds appear in the inner tube at the point where the phosphorus

vapors are condensed by their cold surroundings. The odor of the distillate is alliaceous.

The tube being vertical, the condensed phosphorus will pass down into a receiver, *e*, where it may be converted to phosphoric acid by the action of nitric acid. The phosphoric acid precipitated by magnesium mixture, collected, ignited, and weighed, will determine the quantity of phosphorus.

If no luminosity has been observed after distilling one-third of the material, the remainder may be subjected to a more searching test. The end of the exit tube of the flask should be detached from the condenser at *d*, and immersed in a solution of silver nitrate. The contents of the flask, *c*, are again heated, while a continuous current of carbon dioxide from the generator, *a*, passes through, slowly carrying the phosphorus unoxidized into the silver nitrate, precipitating black silver phosphid, and leaving some phosphoric acid in solution. Should no black deposit appear, the phosphorus may be assumed to be absent. The silver phosphid collected on a filter and washed is suspended in water, and introduced into the hydrogen apparatus employed in the phosphin test described below. The greenish flame is seen even when the quantity is very minute.

Fallacies.—Deductions based upon the detection of phosphoric acid in the distillate when luminosity and free phosphorus have not been obtained may be erroneous. The phosphoric acid may have been brought over by mechanical action.

Interferences.—It can be performed in an organic mixture, but not in the presence of certain chemicals, such as iodine, calomel, and corrosive sublimate. The light will not show in the vapor of turpentine, which may have been given as an antidote. It is not perceived should alcoholic or ethereal vapors arise from the same mixture. Ammonia, chlorine, hydrogen sulphid, sulphur dioxide, petroleum, creasote, and most essential oils interfere with the phosphorescence.

Delicacy.—This test is extremely sensitive, having yielded unmistakable evidence from $\frac{1}{50}$ grain of phosphorus diffused in 3 ounces of fluid (Wormley¹), 1 : 200,000 (Fresenius²).

The Phosphin Test.—Having set up the usual hydrogen-generating apparatus—*i. e.*, flask, pure zinc, and dilute sulphuric acid—the gas is delivered by a three-way tube, having a side jet, to a wash flask containing the suspected organic mixture, and gently heated. The nascent hydrogen acting on the phosphorus, phosphids, or its lower oxids in the mixture will form phosphin (PH_3), a gas which will escape from the heated flask by a tube drawn out to a jet and having a platinum tip. When lighted, the phosphin, if not too concentrated, will burn with a characteristic green color. It may be contrasted with the flame from the side jet, which should be the pale-blue hue of pure hydrogen. If this side jet is greenish, there must have been some phosphorus in the zinc of the generator. To make sure, the greenish flame should be

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 204.

² Fresenius, *Quantitative Analysis*, American edition, New York, 1886.

studied with the spectroscope. If due to phosphorus, it will show one orange band between *C* and *D*, and several green bands (Fig. 27). Both the color of the flame and its spectrum are best developed if the tem-

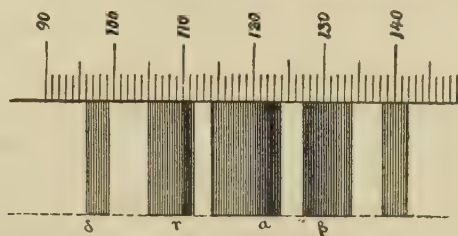


FIG. 27.—The bands represent the green lines of the spectrum of burning phosphorus. They are between the lines *D* and *E* of the solar spectrum (Boisbaudran).

perature of the flame is not allowed to rise too high. This may be accomplished conveniently by allowing the flame to impinge against the bottom of a porcelain dish filled with cold water, or by wrapping the burner with a small strip of cloth saturated with cold water.

Phosphorescence in Hydrogen.—This test for free phosphorus only is best performed with the apparatus of Mukerji (Fig. 28),¹ made from a three-necked Woulfe's bottle of 1 liter capacity, by inserting through close-fitting stoppers a long safety funnel tube (*a*) in one side neck, and a short jet tube (*c*) in the other. Through a loose fitting one at the middle neck rises a tube 11 inches long and $\frac{1}{2}$ inch in diameter, which is closed above by a cork (*b*). From zinc and dilute sulphuric acid in the bottle hydrogen is evolved. Observed in the dark, the gas at the jet should emit no glow, even if commercial chemicals are used. When the chemical action has heated the bottle, the suspected material is introduced through the middle tube or through either neck, quickly closing again with the stopper.

Free phosphorus is vaporized and glows in a sheaf of light at the jet. If the middle cork is removed, the light sinks down through the jet into the bottle, and the glow appears at the outer opening of the middle tube.

Replacing the cork causes the glow to reappear at the jet. If a quantitative estimate is desired, a proper delivery tube may be substituted for the jet and the gas passed into silver nitrate.

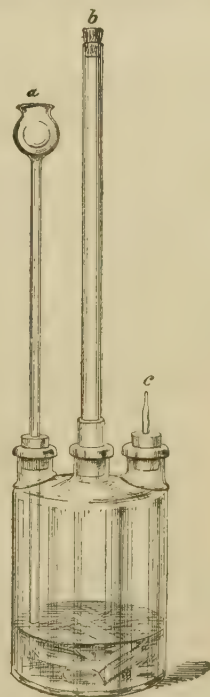


FIG. 28.—Phosphorescence in hydrogen.

¹ Chem. News, 1900, lxxxii, 205.

Special Advantages.—The apparatus is simple, and as no lamp is required for distillation, complete darkness is possible. The amount of air entering by the jet tube is so small in comparison with the quantity of hydrogen continuously evolved that the mixture is never explosive. Before taking apart, the apparatus should be filled with water by the funnel tube.

While this test gives a glow with free phosphorus only, and not with any of its compounds, the *phosphin test* gives a green flame on ignition of the gas when the materials contain phosphorus, phosphids, phosphites, or hypophosphites indifferently. Free phosphorus does not unite with free hydrogen, and the gas here is not phosphin (Roscoe).

Interferences.—Turpentine or ether will prevent the glow in this test. It can be performed in the presence of organic matter, alcohol, iodine, hydrogen sulphide, and many other substances that prevent the glow in Mitscherlich's test.

Delicacy.—Mukerji found the test as sensitive as that of Mitscherlich, getting appreciable effects from 1 : 200,000.

Quantitative Estimation.—Sonnenschein's method for free phosphorus is first to estimate the phosphoric acid by diluting the suspected mixture, filtering a measured fraction, and precipitating with magnesium mixture, estimating as ammonio-magnesium phosphate. Another portion treated on a water-bath with potassium chlorate and hydrochloric acid will have its free phosphorus oxidized to phosphoric acid. This, being estimated, will show an excess over the first portion. The excess is then to be calculated as free phosphorus.

Period for Postmortem Recognition.—Tested by Mitscherlich's method, characteristic phosphorescence has been obtained in putrid organs two months after death and burial. There has been failure, however, to detect the poison even a few days after death, because of the conversion of the phosphorus into ammonio-magnesium phosphate, or some other salt which has no significance to the medicolegal expert.

SALTS OF THE ALKALINE METALS

POTASSIUM CHLORATE

(Chemical formula, KClO_3 .)

This salt is much used in the manufacture of explosives and flashing powders, and in medicine. In the household it is a common remedy for sore mouth and throat, and through a belief in its harmlessness, often leads to injury. It is familiar as whitish flat crystals with a salty, metallic taste, dissolving freely in water.

In 1896 Romanow collected 100 reports of cases of poisoning by it and more than 81 had been observed in Russia up to that date.¹ Witthaus² has collected 143 cases of poisoning from it, 116 of which were fatal; almost all were accidental; 15 were supposed to be suicidal, and 3 homicidal.

¹ Winogradow, *Virchow's Archiv*, 1907, cxc, p. 93.

² Witthaus, *Manual of Toxicology*, New York, 1911, p. 690.

Symptoms.—If used as a mouth-wash it is harmless, but when swallowed in large doses it is an irritant, causing abdominal pain, vomiting, diarrhea, and even collapse. Potter¹ has reported a case of poisoning from two teaspoonfuls taken in two days for sore throat. It caused violent intestinal irritation, with black stools, considerable urinary disturbance with black urine, great prostration, and evidences of grave alteration of the blood. A fatal case in a man of thirty-six years has been reported by Ignatieff.² Soon after taking a teaspoonful of potassium chlorate he developed cyanosis, renal pain, violent vomiting, jaundice, and bloody urine. A band of methemoglobin was seen when the blood was examined by the spectroscope. He died on the evening of the third day. The autopsy revealed enlargement of liver, spleen, and kidneys. There were interstitial nephritis and capsular hemorrhages of the spleen. Willie³ observed a case in which large doses had been taken daily for a month with the production of vomiting, diarrhea, dyspnea, weak heart, and a cyanosis due to chocolate-colored change in the blood. Feckler⁴ reported a case of a lad of fifteen showing the same symptoms from taking 150 grains in saturated solution within six hours.

When absorbed, it has a peculiar destructive action on the red corpuscles of the blood, converting the hemoglobin into methemoglobin and setting up secondary symptoms, such as jaundice, hemoglobinuria, suppression of urine, bloody tube-casts, delirium, coma, and death as a consequence of the acute nephritis or of embolisms of fat.

From a study of his 5 suicidal cases all but 1 fatal Winogradow⁵ states that the bluish-gray tint of the skin and mucosa which marks the collapse is so peculiar as to be diagnostic of the chlorate from ordinary cyanosis. Recovery would seem to be impending in five or ten days, when suddenly attacks of suffocation come on, causing cyanosis and death in one hour. From autopsies and animal experiments the rapidly fatal dyspnea is attributed to fat embolism from the bone marrow. Droplets of fat were found in the lungs, liver, kidneys, and heart.

Fatal Dose and Period.—Fifteen grains proved a fatal dose in a child three years old. Six grams had been taken in a case reported by Zuccola,⁶ with suicidal intent. Hemolysis followed with profuse gastro-intestinal hemorrhages. Blood transfusions gave each time temporary relief, but after the fourth fatal anuria supervened. Dr. Fountain took 1½ ounces with fatal consequences in seven days. If a certain amount is given in divided doses, the effect is more severe than when given in a single dose. Death has occurred in one to five hours, but usually it results from nephritis after several days. While 10 to 12 drams (40–50 gm.) have been taken by adults without decided symptoms, 3 drams (12 gm.) have proved fatal in a healthy subject,

¹ Medical Record, 1895, xlvii, 300.

² Russk. Vrach., 1892, xxxi, 1.

³ Brit. Med. Jour., 1887, i, 1228.

⁴ Cincinnati Lancet and Clinic, 1891, n. s., xxvi, 658.

⁵ Virchow's Archiv, 1907, cxc, p. 1.

⁶ Policlinico, Rome, 1921, 28, p. 82.

and even the almost incredibly small dose of 6 grains (0.4 gm.) in the case noted below which is not free from suspicion of some pre-existing, if unrecognized, nephritis probably induced by the prolonged use referred to. It might be considered as the finishing stroke to a patient already weakened by a succession of lesser trials rather than a single death-blow to a healthy subject. This would also account for the sudden fatality. A woman¹ who had for months used the drug as a gargle probably swallowing some of it each time, inadvertently drank a glassful of the gargling solution representing about 6 grains of the chlorate. In a few minutes she had pains everywhere, cramps, dyspnea, and turned purplish gray, lost consciousness, and died in one hour. The autopsy showed kidney engorgement and extreme hemolysis. The rapidly lethal course may have been due to fat embolism or to asphyxia, resulting from the inability of the altered blood to carry available oxygen.

Treatment.—Having washed out the stomach with the tube or pump, the secondary effects must be combated with appropriate remedies. The kidney complications will require active diuretic treatment.

Postmortem Appearances.—The marks of gastro-enteritis will be found—*i. e.*, a mucous membrane reddened, thickened, and easily detached. Inflammatory changes are seen in the spleen, liver, and especially in the kidneys. These organs are enlarged and dark-brown in color, from the presence of the altered hemoglobin.

Detection.—As the salt is unchanged in the body it can easily be separated from organic matter by dialysis. Having colored the suspected solution with indigo sulphate and acidulated with dilute sulphuric acid, the addition of sulphurous acid will discharge the blue color if the chlorate be present.

POTASSIUM NITRATE

(Chemical formula, KNO_3 , Synonyms, *Niter*; *Saltpeter*.)

This salt occurs in large hexagonal prisms permanent in the air. Under the name "Sal Prunelle" it is to be found molded in small balls. It is used as a remedy for cattle; also in the curing of meat and in the manufacture of gunpowder and other explosives. In the crystalline form it has been taken as a purgative by mistake for magnesium sulphate and sodium phosphate in 8 cases. In 2 cases it has been mistaken for common salt.

In Cured Meat.—In the proportion commonly added to "corned" meat it has neither a full preservative nor condimental effect, but intensifies the red color of the meat which would be otherwise lessened by the action of the other preservatives used. So far as health and digestion are concerned it is safer to omit it from food.² In the "curing" of meat Hoagland³ made it evident that the potassium nitrate formed a bright-red and very stable nitric-oxid hemoglobin. The nitrate

¹ Vienna letter, Jour. Amer. Med. Assoc., December 7, 1907, xlix, 23, 1930.

² Wiley, Proc. Amer. Philos. Soc., May–August, 1908 p., 324.

³ Jour. Agr. Research, 1914, ii, 211.

thus becomes changed to nitrite. Pending further investigation of its wholesomeness it is still legally permissible to "cure" meats with it.

Symptoms.—While doses of 1 dram (4 gm.) cause minor degrees of gastric and intestinal irritation, doses of from $\frac{1}{2}$ ounce to 1 ounce excite acute gastro-enteritis. There are vomiting, abdominal pain, diarrhea, perhaps bloody in character, localized muscular spasms, disturbed respiration and heart's action, and collapse.

Fatal Dose.—Though an adult has died from the effects of 8 grams (2 drams), other cases have recovered from a dose of an ounce or more.

Fatal Period.—Forty-five minutes¹ is the shortest period in which death has taken place; the average duration of fatal cases is somewhat longer.

Windmueller² reports a case of chronic poisoning from a mixture of potassium nitrate and sulphur, the former evidently playing the chief rôle. The interesting points in this case are as follows: A farmer, aged fifty-seven, whose general health had always been excellent, had been suffering for some time with a chronic sacro-iliac arthritis, for which a friend had advised him to take equal parts of sulphur and saltpeter in teaspoonful doses four times a day. He followed this treatment for twenty-six days, taking daily approximately 10 grams of potassium nitrate. He was seen on February 20th, at which time he appeared acutely ill. His eyes were sunken, he had lost much weight, and was very nervous, complaining of intense muscular pain aggravated by motion or touch. Temperature normal or subnormal at all times. Pulse varied from 85 to 95; blood-pressure, 140 systolic and 80 diastolic. Stools distinctly loose. Deep reflexes normal. Pupils reacted to light, accommodation and vision being unimpaired. Blood findings showed a simple but high-grade anemia: hemoglobin, 50 per cent.; red cells, 290,000; leukocytes, 8500. A few poikilocytes were noted. Albumin was present in the urine in substantial quantities, sediment showed a few hyaline and waxy casts and few blood-cells. The amount of the twenty-four-hour urine was only 21 ounces. Patient sleepless for days at a time, and loss of flesh was rapid. Death occurred on March 7th, seventeen days after patient came under treatment. No autopsy could be obtained.

Treatment.—The stomach must be evacuated by emetics, and the stomach-pump or tube be used to wash out the poison. Bland demulcents may be administered, and the tendency to collapse overcome by stimulants and warm applications.

Detection.—As nitrates are not present in the body, the presence of a notable quantity in the gastric contents or other organic mixture would be significant. By adding sulphuric acid the nitric acid is freed and the tests for that acid can be applied (*q. v.*).

¹ Chevalier de Luynes and Devergie, *Ann. d. hyg.*, 1861, 2s, 17, 400.

² *Jour. Amer. Med. Assoc.*, 1921, 77, 858. See McClure and Heap (*Lancet*, 1922, i, 1142) for a discussion of the accidental poisoning of 6 persons by sodium nitrite in the food.

Copper Tests.—Heated in a test-tube with sulphuric acid and copper turnings, nitrates evolve red fumes of nitrogen oxids.

Brucin Test.—Mixed with an equal volume of sulphuric acid, a nitrate solution produces a tint of carmin on the addition of a trace of brucin.

POTASSIUM PERMANGANATE (KMnO_4)

This dark purplish-red crystalline salt is a powerful oxidizer for organic matter, and is thus poisonous to protoplasm and germicidal. The brown stains made by it can be removed by solution of oxalic acid or by dilute hydrochloric acid. It is contained in both Condy's and Darby's fluids which are used to disinfect and deodorize urinals and feces. Concentrated solutions irritate and corrode the tissues and when swallowed induce gastro-enteritis.

With suicidal intent a woman of thirty-seven years took 10 grams of the solid.¹ An hour later the breathing was irregular with pauses lasting twenty seconds, the pulse simultaneously dropping from 72 to 44, but maintaining its strength. This apnea subsided, but the corroding action of the chemical on the throat, as in 2 other cases recorded, caused local phlegmons and pneumonia which were fatal on the fourth day. In the absence of a specific antidote, raw eggs may be given and copious gastric lavage with water carried out.

Potassium bitartrate (cream of tartar) and **potassium sulphate** in excessive doses have acted as poisons, inducing abdominal pain, vomiting, purging, great exhaustion, and fatal collapse. There is no specific antidote for either of them. After evacuation of the stomach the inflammatory and depressing symptoms must be treated as they arise.

BORIC ACID AND BORAX

Borax ($\text{Na}_2\text{B}_4\text{O}_7 + 10\text{H}_2\text{O}$), sodium borate, occurs as colorless prisms or more commonly as a white powder, odorless with a sweetish taste. Its aqueous solution is alkaline and bactericidal. An average dose is 12 grains. As a valuable cleanser and antiseptic it is kept by many households in the medicine chest or the kitchen closet side by side with other white powders. Several cases have been recorded of recovery after doses of $\frac{1}{2}$ ounce taken as an abortifacient.

A fatality after such a quantity was reported in 1895 by Schwyzer.²

Symptoms.—Usually there are salivation, nausea, vomiting, gripes, and diarrhea, signs of local gastro-intestinal irritation which may rapidly culminate in collapse.

If death be delayed soon appear strangury, bloody urine, albuminuria, and tube casts denoting renal and vesical involvement. Nervous phenomena, such as irritation of the skin, mental depression, and delirium may be present. *An illustrative case* was reported by Potter³ of a man who took about 1 ounce of borax by mistake for a saline

¹ Adler, Med. klinik, Berlin, August 16, 1914, 33.

² Jour. Amer. Med. Assoc., February 5, 1921, 76, p. 385.

³ Ibid., p. 378.

laxative. Attacks of violent colic and vomiting with difficulty in swallowing began in fifteen minutes. In addition to the gastro-intestinal irritation there was cyanosis with spasms of choking, in one of which he died three hours after taking the borax. The rapid lethal course did not give time for the other systemic renal, vesical, and cerebral symptoms, and taken with the strangling suggest that edema of the larynx and trachea may have been the immediate cause of death. The absence of gross lesions at the necropsy was ascribed to the lack of sufficient time for their development.

Boric or **boracic acid** (H_3BO_3) occurs in colorless scales or crystals or as a white powder, odorless with a faintly bitter taste, and soluble in 18 parts of water. The average dose is 8 grains.

The local effect of boric acid being very mild, as shown in the favorite eye-lotion, its virtues as a bactericide have led to its use in surgical practice, especially for washing out cavities and sinuses, to prevent septic changes. Cases are recorded of depression, and eruptions of erythema and urticaria following its absorption from wounds and cavities when used too freely.¹ Occasionally graver phenomena have appeared, such as vomiting, diarrhea, bloody urine, and collapse. Fatal results have ensued in a few cases from injecting the solution into abscess-sacs² and from washing out the stomach with it.

The toxicology of boric acid and borax is concerned principally with the use of these agents as preservatives of food. They prevent the growth of organisms that cause fermentation and putrefaction in solid and liquid foods. For meats, they have been mixed with salicylic acid and applied externally. For preserving milk, it was once a common practice to add to 1 quart of milk 10 grains of a mixture of equal parts of borax and boric acid. Naturally these chemical preservatives became objects of suspicion. Were they harmless to the consumers of food so treated? The evidence of some observers was to the effect that they had no injurious action upon the human system. The latest authoritative conclusions are to the contrary. Other observations create a doubt as to their power to inhibit dangerous bacterial growth when only the usual tasteless preservative proportion is added. In 1917 commercial potash fertilizers obtained from a borax lake in California caused damage to germinating maize and potatoes not to be ascribed to any form of disease. Conner's investigation³ showed that the injury was due to borax, of which a very small proportion was poisonous to plants; 2 per cent. in 100 pounds of fertilizer per acre. The amount of borax sufficient to act as a plant poison was small compared with that of either arsenic or copper.

On the one hand, we have the researches of Chittenden⁴ and of Liebreich⁵ with dogs fed upon articles containing borax and boric acid.

¹ Northwestern Lancet, 1888, viii, 22.

² Medical News, 1882, xl, 571; 1883, xliii, 199.

³ Circ. 84, U. S. Dept. Agr., 1920; Jour. F. I., 1920, p. 670.

⁴ American Journal of Physiology, 1898; also Best, Jour. Amer. Med. Assoc., September 17, 1904, p. 805.

⁵ Vierteljahrsschrift für gericht. Med., 1901; also Lancet, January 6, 1901.

In both series the digestion of the food was not notably impaired and the animals gained in weight. The same result followed the experiment made by Liebreich upon rabbits and guinea-pigs. No injury appears to have followed the administration of boric acid to pigs, calves, and children by the British Commission.¹ Tunnicliffe² made experiments from which he inferred that neither of them affected the health of the children experimented on. Vaughan and Veenboer³ conclude that in the small amounts required for preserving cream and butter, and that used as an external dust on hams and bacon, both boric acid and borax are unobjectionable from a sanitary standpoint.

On the other hand, the experiments made by H. E. Annette⁴ led him to an opposite conclusion. He found boric acid injurious to kittens, and naturally assumed that the use of milk containing it might be hurtful to young infants. Foster and Schlenker⁵ found that albumin digestion was impaired by boric acid, which also produced increased desquamation of the intestinal epithelium. Doane and Price⁶ made experiments on calves which indicate that borax and boric acid in milk retard digestion to a slight extent.

Wiley's⁷ experiments upon man proved that "both boric acid and borax when continuously administered in small doses for a long period or when given in large quantities for a short period create disturbances of appetite, of digestion, and of health." The controversy has not been free from suspicion of bias owing to the interest taken by the borax and the meat packing industries whose profits are imperilled.

The effects of boric acid as a food preservative are to be viewed from a new angle, since Bernstein's^{8, 9, 10} series of experiments which showed that boric acid 0.3 per cent. (20 gr. to 1 lb.) prevents or checks the growth of yeasts, of organisms of the *proteus* group, and of some harmless saprophytes. Except to retard and lessen slightly, it affected not at all the growth of the *coli* group, *Bacillus typhosus* and *Bacillus enteritidis* (Gärtner's meat-poison bacillus). Hence with this strength of boric acid dangerous stale meat and even that in which decomposition has begun can be made inoffensive to smell and taste and marketed in flavored sausages.

If Gärtner's bacillus has gained access it will have had several days to grow unhindered by saprophytes, and without the warning smell of decay given by stale meat when "unpreserved." In this country (United States) to add borax or boric acid to milk is forbidden by a law, the vigorous execution of which has put an end to the practice.

¹ Lancet, 1901.

² Journal of Hygiene, 1901.

³ American Medicine, March 13, 1902.

⁴ Lancet, November 11, 1899.

⁵ Quoted in report of Kober on Milk Preservatives, United States Senate Commission, 1902.

⁶ Bulletin No. 86, Maryland Agricultural Experimental Station, September, 1902.

⁷ Circ. No. 15, U. S. Dept. Agr. Bureau Chem., p. 27, 1908.

⁸ Brit. Med. Jour., April 16, 1910;

⁹ Jour. Amer. Med. Assoc., May 14, 1910, liv, 1617.

¹⁰ Ibid., p. 1654.

According to sanitary officials the wisest course would be to avoid their use entirely, since the most conclusive evidence has been adduced that they are not free from harm in the amounts as commonly used for preserving food, and they give a false sense of security.

Normal Boron.—Bertrand's¹ official note to the Academie des Sciences reports the constant presence of extremely small quantities of boric acid in the ashes of natural animal and vegetable food-stuffs. In a kilogram of normal dried fruit, such as apricot, was found 112 mg., strawberries 56 mg., cherries 112 mg., black raisins 228 mg., pears 28 mg. It was in almost all normal vegetables, such as carrots, onions, and turnips from 56 to 112 mg. per dry kilogram. Finding traces of boric acid in foods is not sufficient to prove that it has been added as preservative. A quantitative analysis is necessary to prove excess over the trace normal to living cells.

Detection of Boric Acid in Meat.—*Jorgensen's test*² makes use of the property of neutralized boric acid to take on an acid reaction after treatment with glycerin. The meat is made strongly alkaline with sodium hydroxid, extracted with hot water for several hours, and the extract filtered. The filtrate is evaporated to dryness, incinerated, and the ash dissolved in sulphuric acid. By warming, the carbon dioxid is removed, and on cooling the solution is neutralized by an alkaline hydroxid, using phenolphthalein as indicator.

To 50 c.c. of the neutral fluid 25 c.c. of glycerin are added, and the mixture titrated with decinormal sodium hydroxid solution without regard to the phosphates. The end-reaction is made more definite by the addition of ethyl alcohol.

Detection in Milk.—*Hird's Test.*—Place in a porcelain dish 1 drop of the milk with 2 drops of strong hydrochloric acid and 2 drops of a saturated turmeric tincture. Dry this on a water-bath, cool, and add a drop of ammonia by means of a glass rod. A slaty-blue color changing to green is produced if borax is present. A drop of milk containing $\frac{1}{1000}$ grain of borax will give this reaction.

Flame Test.—With alcohol boric acid forms a volatile ester which burns with a *green* flame. Material suspected of containing boric acid is put in a capsule and covered with sulphuric acid. Alcohol is poured over the mixture which is then heated until it takes fire. The *green* color of the flame is characterized by four lines in the spectrum in the yellow, green, and blue.

SODIUM SILICATE

(Chemical formula, $\text{Na}_2\text{Si}_4\text{O}_9$; Synonyms, *Water Glass*, *Soluble Glass*.)

Commercial "water glass" is prepared by heating to the melting-point a mixture of sand or quartz, dry sodium carbonate, and charcoal. Thus fused together the product is run into water, which curdles it into glass-like porous lumps, which can be dried and kept or slowly

¹ Jour. Amer. Med. Assoc., February 14, 1914, lxii, 549.

² Ztschr. f. angew. Chem., 1897, 10, 5; in this connection see Beythien and Hempel, Ztschr. f. Untersuch. d. Nahrungs. u. Genussm., 1899, 2, 842.

dissolved in boiling water. This solution was formerly official as *Liquor Sodii Silicatis*, U. S. P., a semitransparent, yellowish, viscid liquid, odorless, with a saline and sharp alkaline taste and reaction. The thick liquid dries rapidly, growing hard and tough like glass. It is used as a cement; to make bandages immovable and for the manufacture of artificial stone. It is antiseptic, preventing alcoholic fermentation and putrefaction. Hence its use in the household for preserving eggs into winter by keeping them submerged in it. Recent analyses in Germany show frequent adulterations, especially with objectionable sulphur compounds and with sodium sulphate.

Symptoms.—When administered to dogs by the mouth it caused inflammation and ecchymosis of the gastro-intestinal mucosa, congestion of the kidneys with infarction of the tubules. By intravenous injection it was fatal. A dose of 15 grains (1 gm.) to rabbits induced alterations in the blood and fatty degeneration of the liver. Eichhorst¹ reported a case of a man who recovered after drinking by mistake for wine, 200 c.c. (6.75 fl. oz.) of it. Prompt vomiting relieved him of some of the poison, but enough remained to irritate the alimentary mucosa, causing gray discoloration, vomiting, diarrhea, severe abdominal pain, and occult bleeding. Excretion by the kidneys caused albuminuria, tube casts, sugar, acetone, and blood in the urine for a few days. At the same time there were high temperature and blood-pressure with lymphocytosis.

Treatment.—An ice-bag was applied to the neck, and the gastric irritation combated by giving pieces of ice, iced milk, and acacia mixture. It is not unlikely that commercial samples might be caustic from excess of alkali. If a small portion applied to the hand produces the local effect of a strong alkali, the treatment might well include weak lemon juice or vinegar with oils and milk.

LITHIUM SALTS

Lithium chlorid (LiCl) and lithium carbonate (Li_2CO_3) are sometimes present in mineral waters and in the ashes of our blood, milk, and food vegetables. The salts closely resemble the corresponding ones of sodium. They were formerly used in medicine as supposed solvents of uric acid deposits and calculi. Good² made an experimental study of the action of lithium chlorid on cats and dogs. He found that it was rapidly absorbed from the stomach. Shortly after administration of a large dose, whether by mouth or subcutaneously, the animals were seized with nausea, vomiting, diarrhea, and tremors. They died sooner or later with gastro-enteritis, inducing progressive prostration and wasting. With small doses given continuously to cats the colonic mucosa was found congested, sometimes hemorrhagic and ulcerated.

Elimination was by saliva, feces, and urine. By the urine it was slow and did not cause renal or vesical symptoms. The large excretion

¹ Schweiz. med. Wehnschr. Basel, November 25, 1920, 50, 1081. See Gye and Purdy (Brit. Jour. Exp. Path., 1922, 3, 75 and 86) for poisonous properties of colloidal silica.

² Amer. Jour. Med. Sci., February, 1903, cxxv, 273.

through the walls of the bowel excited irritation, as is the case in poisoning by the heavy metals.

In an investigation, the conclusions of which were confirmed by repetition several months later, Cleaveland¹ took 60 to 90 grains or 4 to 6 grams daily of lithium chlorid, and on both occasions experienced symptoms differing from those reported by Good in the absence of gastro-enteritis. He suffered general muscular weakness, tremors, dizziness, and fulness of the head, blurred vision, ringing in the ears, but no anorexia, abdominal pain, or diarrhea. While Good's experiments were confined to lower animals that could not give evidence of subjective symptoms or those referable to the special senses, he quoted a case where lithium carbonate in 15 or 20 grains (1.0 to 1.3 gm.) doses caused gastro-intestinal irritation in man, and so far confirmed his observations on animals. Cleaveland's research alone would lead to the conclusion that lithium intoxication in man is wholly systemic, as stated above. A synthesis for these opposed views may be found in the possibility that in Cleaveland's case there may have been unusual power of gastro-enteric resistance to the toxic agent.

Test.—Lithium is identified by the red color of its flame. The spectrum shows two bright lines, one red and the other yellow, distinct from the sodium line.

ALUM

(Chemical formula, $\text{AlK}(\text{SO}_4)_2 + 12 \text{H}_2\text{O}$. Synonym, *Alumen*.)

The name "alum" is given to both the potassium-aluminum and the ammonium-aluminum sulphates.

Toxic Symptoms.—Excessive doses of this salt have produced irritant symptoms sometimes ending in death. Kramolik² reported the case of a young man, aged thirty years, who by mistake drank a mouthful of a 10 per cent. solution of alum. Neither the mouth nor the throat showed any marked reaction to the irritant, but the patient vomited thirty-nine times within the forty-eight hours following. Palpation of the stomach was painful. Mucus was found in the vomitus, mingled with blood, imparting a chocolate color to the mass. The urine was stained by blood, and showed morphologically numerous red blood-cells, a few leukocytes, and a few hyaline casts. Traces of albumen were also present. The patient was ill for at least thirteen days.

In Baking Powders.—The medicolegal interest in it is practically limited to the question of its action and that of aluminum sulphate when used as a constituent of certain baking powders which are consumed by the ton in domestic bread-making. In these powders sodium bicarbonate furnishes gaseous carbon dioxid, which is liberated by the action of the aluminum sulphate present, leaving in the bread sodium sulphate and aluminum hydroxid. At one time the view was held that the fact that many thousands of persons have used these powders without any marked injury, local or systemic would indicate that though

¹ Jour. Amer. Med. Assoc., 1913, ix, 722.

² Pester Medicinisch-chirurgische Presse, 1902, xxxviii, 241; see Spofforth (Lancet, 1921, i, 1301) for a case of poisoning due to working with heated aluminum.

the aluminum hydroxid be changed to a soluble chlorid by the gastric juice, the amount absorbed must be within the limits of toleration by many individuals. In bread-making, if 2 teaspoonfuls of alum baking powder be used the aluminum residues in a loaf amount to 165 grains (11 gm.). That the use in food of any aluminum compound is hurtful was the conviction of Gies,¹ who urged their exclusion on the basis of his own experiments on plants which showed that even when present in very minute proportions they were protoplasmic poisons.² The experiments of Mallet³ made on man went to show that the aluminum of ingested bread made with baking powder containing it was, under the action of the gastric juice, present in dissolved form in the stomach of the subjects. It is likely that the action of this soluble chemical would be deleterious to the gastric processes. Persons with temporary illness or those with permanently feeble digestion would suffer greater detriment than the many in health or of average peptic strength, whose power of resistance would enable them to withstand the tax without obvious harm. It is probable that the insidious strain repeated daily would in time be hurtful, and yet the cause of this effect go unrecognized. To test the question of absorbability into the blood of the aluminum in bread made from alum baking powder, Steel⁴ experimented on dogs and proved that it did pass into the blood stream from the digestive tract, thus establishing the facts that the aluminum residue is not insoluble, and that it may exert some systemic effect, though that escape notice at the time. For these reasons it is just to demand that positive proof be furnished that these chemicals foreign to the normal body are harmless. This proof beyond a reasonable doubt is still lacking. Siem⁵ in his researches found that alum given to dogs and cats subcutaneously caused paralysis of sensation and motion, with fatty degeneration of the liver and kidneys. The safest view is to hold aluminum compounds as an unnecessary addition to bread, and certainly of no value as a food. Its presence in any but the smallest amount should be considered proof of adulteration.

Detection.—Having incinerated the organic matter in a platinum dish, the ash should be treated with hydrochloric acid, excess of acid removed by heat, a few drops of nitric acid added, and a final solution in hydrochloric acid boiled and filtered.

This solution is not changed by potassium ferrocyanid or hydrogen sulphid, as are solutions containing the heavy metals. With potassium hydroxid a white precipitate falls, redissolved by excess, whereas an excess of the reagent does not affect the precipitate from a solution of the alkaline earths.

Logwood Test.—The most convenient test for alum in bread is made with a freshly prepared tincture of logwood. This tincture is made by digesting 5 grams of freshly cut logwood chips with 100 c.c. of alcohol.

¹ Jour. Amer. Med. Assoc., September 2, 1911, lvii, 816.

² Amer. Jour. Physiol., 1906, xv.

³ Jour. Amer. Med. Assoc., 1911, lvii, 817.

⁴ Amer. Jour. Physiol., 1911, xxviii, 94.

⁵ Schmidt's Jahrbuch, 1886, cexi, 128; Inaug. Dissert., Dorpat, 1886.

Having diluted 5 c.c. of the logwood tincture with 90 c.c. of water and added 5 c.c. of saturated solution of ammonium carbonate, the mixture is *immediately* poured over 10 grams of bread in a glass dish. After five minutes the liquid is poured off, the bread slightly washed, and dried at 100° C. A lavender or dark blue color denotes that alum is present. Pure bread is at first reddish, fading to a yellow or light brown.

Delicacy.—This test yields a distinct blue with 0.02 per cent. of alum, or 7 grains in a 4-pound loaf.

Fallacy.—Several other mineral adulterants produce a somewhat similar reaction.

Test for Aluminum Sulphate in Baking Powder.—A small quantity of the suspected substance is burned to an ash, which is then treated with boiling water and filtered. If the filtrate yield a flocculent precipitate when treated with ammonium chlorid, then aluminum is present in the sample.

THE HALOGENS

IODIN

(Chemical symbol, I; Synonym, *Iodum*.)

Elementary iodine is a bluish-black solid crystallizing in soft, metallic-looking scales which have an unpleasant taste. At ordinary temperatures it gives off slowly an irritating, invisible vapor. Heated to 220° F. it liquefies and then breaks into a rich, violet-colored vapor. Very sparingly soluble in water, it dissolves freely in alcohol, ether, carbon bisulphid, and an aqueous solution of potassium iodid. The tincture and the liniment are dark brown fluids used as external applications. By mistake these have been taken internally, causing accidental poisoning, which occurrence, however, is very rare. We are indebted to Baumann¹ for the demonstration that iodine is a normal constituent of some animal tissues, especially the thyroid gland.

Symptoms.—It acts as a powerful irritant upon the stomach and bowels, causing pain in the mouth, throat, and stomach, vomiting and purging, extreme thirst, fainting attacks, and collapse. When applied by surgeons freely to absorbing surfaces, it may cause systemic disturbances, such as headache, dizziness, mental trouble, along with the above gastric symptoms brought about indirectly. Its elimination by the kidneys involves that organ in inflammation, which may end in suppression of urine. Bellot² reported a case of attempted suicide in a woman who took a half-glass of the tincture. Nausea and burning pain in the throat immediately followed. A quart of water was given, but there was no vomiting for an hour, when a dark, thick fluid was ejected, followed by clear blood. In spite of treatment by milk and starch, in a few hours she had abdominal pains and tenderness, dizziness, and syncope. Entire recovery ensued in a few days. The urine was normal. No iodine could be detected in the urine, saliva, or sweat.

¹ Ztschr. f. physiol. Chem., 1895, xxi, 319.

² La Méd. Moderne, Paris, 1893.

In an experimental investigation upon animals Luchardt, Koch, Schroeder, and Weiland¹ found that when the vapor of iodine was inhaled it caused irritation of the air-passages, and in large amounts led to death in twenty-four hours from acute and rapid pulmonary edema. They advised against any therapy by iodine inhalation, and consider it positively contraindicated in pulmonary diseases.

Fatal Dose.—Death has resulted from 1 fluidram of the tincture, containing less than 2 grains of the element. Ten or 20 grains of the solid would probably be fatal. Recovery has followed a dose of 1 fluid-ounce of the tincture.

Fatal Period.—While death has occurred in twenty-four hours, in cases of poisoning from external application it will be delayed for several days. A boy eleven years of age under the care of Culpepper² was poisoned by absorption of iodine from a raw surface extending on both legs from the knees to the feet. On the sixth day he died, having suffered from suppression of urine, hemorrhagic stools, vomiting, and purging. Iodine was found in the vomited matters.

Treatment.—Large drafts of tepid water will assist in evacuating the stomach. The antidote is starch in some form, best given in decoction, such as the clear starch of the laundry or as gruels, boiled rice, or arrow-root, given as long as the vomited matters have a blue color.

Postmortem Appearances.—The morbid changes found are such as attend gastro-intestinal irritation, leading to inflammation and excoriation.

Detection.—By agitating organic matters or an aqueous solution of iodine with carbon bisulphide the iodine is separated, making a violet colored solution. If the iodine is combined, a very small quantity of chlorine-water must be used to liberate it. A decoction of starch which has been allowed to cool gives a dark blue color, due to the formation of iodide of starch. The yellow stains on the skin and lips are removable by ammonia, which would only deepen the stain of nitric acid.

"Iodism."—Excessive doses of iodides or the persistent use of average doses may induce the symptoms of "iodism." Fatal cases are rare. A typical one was reported by Wolf.³ The patient was unusually susceptible, owing to the fact that she was suffering from renal disease and cardiac hypertrophy. She took 6 grains four times in one day. The face swelled, and acne and pemphigus appeared, although no more medicine was taken. In twenty-four hours the eruption involved the mucous membrane of the upper air-passages. On the fourth day there was bloody diarrhea. The facial pemphigus passed into deep ulcers. In eight days she died in collapse.

BROMINE

(Chemical Symbol, Br; Synonym, *Bromum*.)

This element is a dark, reddish-brown liquid, which vaporizes in red fumes of an unpleasant odor and highly irritating to the mucous mem-

¹ Jour. Pharm. and Exper. Therap., March, 1920, 15, 1.

² Therap. Gazette, 1888, 3 S., iv, 225.

³ Berlin. klin. Wochenschr., 1886, xxiii, 578.

brane of the nose and air-passages. The saturated solution in water is used as a chemical reagent. Alcohol and ether are the best solvents for it. Like iodine, bromine has been found as a normal constituent of animal tissues, including those of man, but apparently not localized as is iodine. The quantities reported average much less than a milligram per 100 grams of fresh tissue.¹

Symptoms.—Its vapor when inhaled causes symptoms of violent catarrhal inflammation of the air-passages, with cough, constriction of the chest, and hemoptysis. According to Marino² respiration of bromine vapor causes diminution of the number of red blood-cells and of the hemoglobin content of the blood, while it produces a marked increase in the number of leukocytes. It acts vigorously as a caustic on organic matter, producing, when swallowed, pain in the mouth, throat, and stomach, with eructation of the peculiar offensive vapor. Its powerful local action may bring on collapse in a few hours. Liquid bromine was used in the World War as filler for hand grenades. By direct contact it corroded the tissues and its vapor asphyxiated. They that survived breathing it suffered from severe irritation of eyes and air-passages.

Fatal Dose and Period.—Very few cases of death have been reported. One was caused by 1 ounce of bromine. In another fatal case a child of ten took what was calculated to be about 2 grains of bromine. Fatal collapse has come on within seven hours.

Treatment.—Complete evacuation must be secured by emetics and the stomach-pump. The chemical antidotes are protectives, such as mucilaginous drinks made from starch, arrow-root, barley, rice, flour, or meal.

Postmortem Appearances.—A dark brown stain marks the point of local action; the mucous membrane is inflamed, softened, loosened, or even corroded.

Detection.—The element may be identified by its color and odor. If it is present as bromide, the bromine must be freed by adding a little chlorine-water. When bromine-water is shaken with chloroform the latter takes up the bromine and separates it in a brownish-yellow layer. Starch-water forms the bromide of starch, which is of a deep yellow color.

"Bromism."—This name has been given to the poisonous effects of long-continued dosing with bromides. The symptoms are the fetid odor of bromine on the breath, mental dullness, nervous depression, muscular weakness, absence of sexual feeling, eruptions of acne, bullæ, and pustules. When pushed to the extreme the bromides have caused exhaustion and fatal heart failure. Eigner³ reported a case in a woman nineteen years of age, an epileptic, who, without the sanction of a physician, increased the dose of potassium bromide until she became weak, nervous, wakeful, tremulous in all her movements, and com-

¹ Sep Damiens, Bull. Soc. Chim. Biol., 1921, iii, 95; Bull. sci. pharmacol., 1921, 28, 37.

² Arch. farm. sper., 1920, 29, 48; Chem. Abs., 1921, 15, 1763.

³ Wien. med. Presse, 1886, xxvii, 815.

plained of loss of memory, headache, and vertigo. She had fetid breath, coryza, and salivation, became delirious, had lobular pneumonia, and died. Van der Bogert¹ has reported a case of bromid poisoning, characterized by marked skin eruptions in a child six months old, arising from the milk of the mother.

CHLORIN

(Chemical Symbol, Cl; Synonym, *Chlorum*.)

The gas is two and a half times heavier than air, has a greenish-yellow color, a peculiar, irritating smell, and is very energetic chemically. Used in the arts as a bleaching agent and in the household as a disinfectant, it is usually generated from "bleaching salt"—*calx chlorata* of the Pharmacopeia.

Symptoms.—When inhaled in small amounts it causes a suffocative feeling and cough. If taken undiluted it causes difficult breathing, a painful sense of tightness in the chest, and violent cough with hemorrhage. Indirectly the nerve-centers are involved, producing stupor and even heart failure. A fatal case occurred at Cornell University in Ithaca, in 1894, in an old woman the victim of a practical joke. During the World War on the Ypres front, 1915, liquid chlorin in condensers was released in clouds which clung to the ground, and when blown in the right direction by the wind gave great distress to the enemy in the trenches. It caused dyspnea, cough, occasional vomiting, and cyanosis, severe and persistent. Postmortems revealed laryngitis, edema of the lungs, and emphysema.

Fatal Dose.—Fatal consequences are not apt to occur unless the subject is in delicate health, and the gas is taken with little admixture of air.

Treatment.—Fresh air must be given at once, and the pain relieved by the inhalation of ether. The symptoms of acute bronchitis, narcotism, and enfeebled heart's action must be treated by appropriate remedies.

Detection.—The gas can be recognized by its odor and its bleaching action on moist litmus-paper. As chlorin-water it has the same properties, and, in addition, dissolves gold-foil and yields a white precipitate with silver nitrate, insoluble in nitric acid, but soluble in ammonia.

FLUORIN

(Chemical Symbol, F.)

A trace of fluorin is *normal* to milk, eggs, teeth, bone, and other animal tissues.² In the manufacture of "superphosphate" fertilizer animal refuse is treated with dilute sulphuric acid. The fluorids and silicates evolve the excessively irritating and poisonous gas *silicon tetrafluorid* (SiF_4). To prevent the deleterious consequences of inhalation the mixer and all conduits should be air-tight and the vapors conveyed through washers and purifiers to the furnace shaft.

¹ Amer. Jour. Dis. Children, 1921, 21, 167.

² Jodbauer, Ztschrft. f. Biol., 1901, v, 487.

Hydrofluoric acid (HF) is a colorless gas, soluble in water and imparting to it a fuming, corrosive power of irritating the air-passages and causing painful wounds of the skin. Inhaling ammonia vapor and washing with ammonia-water are the remedies for these. Four fatal inhalations have been reported,¹ among them two noted chemists, Nicklès of Nancy and Louyet of Belgium.

Sodium fluorosilicate (SiFNa_2) in solution has decided antiseptic properties, but when ingested alone or as preservative of food causes nausea, eructations, vomiting, and slow pulse.

Sodium fluorid (NaF) in weighable amounts is poisonous to all forms of life, high and low, owing to its precipitating from the active state the calcium salts, which are essential to the healthy equilibrium of protoplasm. One part of this salt in 200 stops the growth of bacteria. It delays putrefaction when 1 part is added to 500 of a fermentable fluid, such as the sour mash of distilleries and when used as preservative of foods. It has been added to bottled beer to prevent the lactic, acetic, and butyric fermentations. While the amount in a single bottle may do no detectable harm if the preserved beer is used as a habitual beverage, toxic effects are noted.

Symptoms.—Schwyzer,² experimenting on animals, found that continued very small doses of 1 to 2 mg. per kilogram of body weight were poisonous, causing increased coagulability of the blood, tendency to venous thrombosis, and irritation of the bone-marrow. The fluorin displaces chlorin which is excreted by the kidneys, and thus may become deficient in the body; while the bone-marrow, invaded by lymphoid elements, loses fat. Upon man its dilute solution irritates the mucosa: of the eye, causing conjunctivitis; of the digestive tract, causing salivation, retching, nausea, vomiting, gastro-enteritis, ending in corrosion. The later developments are neuralgias, cardiac weakness, dropsies, phlebitis, painful urination, albuminuria.

Fatal Dose.—In man no fatality from sodium fluorid has been reported, but in dogs³ intravenous injections of 0.05 to 0.1 gram per kilogram were fatal.

It has been noted⁴ that certain baking powders containing the acid sodium phosphates may show fluorin, 0.04 to 0.5 per cent. It is a constituent of "phosphate rock," sometimes used in producing the acidic ingredient of the powders. The maximal limit of the possible daily intake by an adult is estimated at 0.77 to 78.1 mg. ($\frac{1}{8}$ – $1\frac{1}{8}$ gr.), varying with the sample. While proportional doses to rats had no effect,⁵ larger doses caused progressive impairment of growth and food-intake, ending in a permanently subnormal condition. The figures quoted show that no perceptible injury would be likely from the amounts of fluorin commonly found in these certain baking powders:

¹ King, Tr. Path. Soc., London, 1873, xxiv, 98; Stimson, Brit. Med. Jour., 1899, ii, 1145; Witthaus, Man. Toxic., 1911, p. 309.

² Biochem Ztschrft., 1914, lx, 32.

³ Sollman, Text-book of Pharmacol., 1913, p. 573.

⁴ Jour. Amer. Med. Assoc., June 11, 1921, 76, 1688.

⁵ Sollman, Schettler and Wetzel, Jour. Pharmacol., April, 1921, 17, 197.

The possibility of harm from larger amounts present, owing to careless preparation, should not be ignored, since it has been shown that daily doses of 15 mg. per kilogram of body weight are notably toxic.

Elimination.—With difficulty absorbed from the alimentary tract it is very slowly excreted by the urine. The insoluble calcium fluorid formed by it is stored in the liver, skin, and other tissues. Masses of these crystals accumulating in the bones impair their nutrition and make them whiter, harder, and more brittle.

Treatment.—The indication is to make the soluble sodium salt inert by change to the insoluble calcium fluorid. This is done by copious and repeated gastric lavage with lime-water and weak solutions of calcium chlorid followed up with a course of calcium chlorid. An accidental case on record¹ illustrates these points very well. An infant girl of nineteen months swallowed an unknown quantity of "Peterman's Roach Food," which is asserted to contain 40 to 50 per cent. sodium fluorid. Nausea and vomiting began at once. Frequent stomach washings were given, using in this way a gallon of lime-water with calcium chlorid in solution. Apparent early recovery was followed seventy-two hours later by albumin, renal tube casts and a few blood-cells in the urine. These symptoms joined to fever and an abnormal blood count suggested high colonic irrigation and a dose of castor oil. By the fifth day fever and albuminuria disappeared, and the patient was discharged at the end of the week. Seven persons were poisoned by pastry in which by mistake sodium fluorid was used for sodium bicarbonate.² The amount absorbed in each case was about 0.228 gram except in one case, estimated to have taken 0.456 gram. Attacks of gastralgia, nausea, and vomiting lasted for three to six hours, except in the one patient that took the larger dose, who suffered for twelve hours. For thirty-six hours general weakness was the sequel, followed by recovery.

Detection.—The presence of a trace of fluorin is not to be regarded as significant of toxic amounts. It is *normal* to animal tissue, especially teeth and bones. Fluorin in organic matter, which does not contain silica, can be identified by adding a small amount of sodium hydroxid and incinerating. The ash with concentrated *sulphuric acid* may be warmed in a platinum crucible, covered with glass only partly coated with wax or paraffin. A rough or etched surface on the uncoated glass denotes fluorin. If the material contains silicates, then the same test evolves gaseous *silicon fluorid* which does not corrode glass. However, if a glass rod wet with a drop of water be held over the crucible evolving gas the water shows a film or pellicle of silicic acid which could only have been volatilized in the form of a fluorid.

¹ Stanton and Kahn, Jour. Amer. Med. Assoc., June 12, 1915, lxiv, 1985.

² Vallée, Jour. Pharm. Chim., 1920, 21, 5.

TELLURIUM

(Chemical Symbol, Te.)

No fatalities have been reported from tellurium poisoning, though characteristic symptoms are due to it. Until recent years it was classed as a rare metal of no practical value. It is growing in use as a reducing agent for steel and for coloring glass. It is present free or as tellurid in certain ores of gold, silver, selenium, and iron. It exists in the dross of electrorefining ores of copper and lead. In separating lead the workers run a risk from fumes of hydrogen tellurid (H_2Te), and dust of tellurium oxid (TeO), and compounds of telluric acid (H_2TeO_4). Physically, tellurium resembles metals, but chemically is allied to oxygen, sulphur, and selenium. Strong acids acting on tellurids form hydrogen tellurid analogous to hydrogen sulphid and hydrogen arsenid. It resembles these in being a poisonous gas with an offensive odor. While this and other compounds are dangerous to health when encountered in industry, the symptoms are not usually severe.

Symptoms.—In their investigation Shie and Deeds¹ found the earliest sign is the persistent garlic odor of the secretions and excretions, possibly due to the formation in the body of methyl tellurid. Afterward appear suppression of the sweat, the saliva, and the acid of the gastric juice. The skin is dry and itching; there is a bitter taste and a disagreeable odor of the breath followed by anorexia, nausea, vomiting, indigestion, and constipation. Drowsiness to a notable extent is frequent. The secondary toxic effects are impaired nutrition, weakness, and wasting. With a history of working in telluriferous ores, the diagnosis hangs on the offensive odor of garlic, the dry skin and mouth, and tellurium in the urine and feces. After lethal doses given to animals death is preceded by dyspnea, convulsions, and coma.

Treatment.—The symptoms are to be treated as they arise with diaphoretics, laxatives, and diuretics to assist in elimination. The prognosis is good if withdrawal is prompt.

Prevention.—In order to insure freedom from hazards, injurious fumes and dust should be confined at their source and removed. If this be not possible, free ventilation and respirators are needed, with daily shower-baths and changes of clothes.

Postmortem Appearances.—In animals the autopsy reveals inflammation of the alimentary mucosa, intestinal hemorrhage, hyperemia of the organs, hemolysis, and parenchymatous nephritis.

Detection.—The precipitate by *hydrogen sulphid* from acid solution of tellurium is treated with ammonium sulphid which dissolves tellurium with several other metals. These dissolved sulphids are again precipitated by hydrochloric acid, and after washing heated with concentrated hydrochloric acid which dissolves arsenic, antimony, and tin, but leaves tellurium undissolved. This residue is dissolved by nitric acid, as an acid to be neutralized by potassium hydroxid. Evaporated to dryness, tellurium is recognized by melting with *potassium cyanid* and dissolving in water which turns red from potassium cyanotellurid.

¹ U. S. Pub. Health Repts, 1920, 35, 939.

Sodium Bisulphite Test.—Treat the suspected substance with hydrochloric acid containing the least possible chlorin and heat to expel excess of chlorin, add sodium bisulphite, and filter. Tellurium gives a black precipitate on filter.

Sulphuric Acid Test.—If present in feces or urine in large amount, the dried substance heated in concentrated sulphuric acid gives the garlic odor and a deep crimson color, which disappears if the acid is too hot or if it be diluted after cooling.

Biological Test.—The “arsenical mold,” *Penicillium brevicaulis*, is a living reagent, converting tellurium, selenium, and arsenic solid compounds into volatile odorous substances. That from tellurium is like that from arsenic, but selenium has more of mercaptan odor. Having excluded arsenic by previous appropriate tests, Gosio’s method (p. 229), using crumbs of bread with a culture of the special mold, yields the garlic odor from very small amounts of tellurium.

THE HEAVY METALS

SILVER

(Chemical Symbol, Ag; Synonym, *Argentum*.)

Metallic silver is not poisonous, as is often demonstrated by the use of silver wire for sutures and the absence of injurious consequences when silver coins have been swallowed accidentally. Cases of acute poisoning are limited to silver nitrate.

Silver nitrate when pure crystallizes in colorless rhombic plates, freely soluble in water, and having a metallic taste. In medicine an official form, known as *argenti nitras fusa* (lunar caustic), is applied as a superficial escharotic, correcting local diseased states.

Of 8 cases reported¹ due to swallowing of the caustic, 5 were the results of accident in children (one of these was fatal) and 3 in adults. One was a woman of fifty-one years who died in three days from swallowing in broken doses 50 grains of silver nitrate. Another was a would-be suicide, who recovered after taking 1 ounce; the third was a paranoiac who died from swallowing 3 sticks of lunar caustic.

Symptoms.—The contact of the caustic causes instant pain in the throat and stomach, prompt emesis, and later purging of bloody matters. After absorption takes place nervous symptoms supervene, such as vertigo, spasms, disturbed respiration, and coma.

Chronic Poisoning.—An interesting case due to repeated cauterization has been described by Tolmacheff. A small granuloma of the foot having been removed, the spot was cauterized with solid “caustic” fifteen times in two months. At a later period fifteen more applications were made in two and a half months. At this point emaciation began, followed in a few weeks by left-sided hemiplegia, with ecchymoses under the eyelids. The patient’s face turned a leaden color, the sclerotics were discolored, many brownish-black spots appeared all over the body, and a blue line was seen on the gums. Similar discoloration patches,

¹ Witthaus Toxicology, 1911, p. 304.

oval and about the size of apple-pips, were found in 800 silver workers in Berlin.¹ They were attributable to absorption through some abrasion of the hands. The general health was unaffected. Microscopic examination of the patches proved them to be due to deposit of metallic silver in the tissues.

A leaden bluish discoloration of the face and possibly of other parts of the body is sometimes brought on by the medicinal use of small doses of silver nitrate given for a long period. No manner of treatment is of any avail to remove this discoloration. Goldstein² reports argyria of the face, lips, and hands following the spraying of the throat with argyrol twice daily for a year.

Fatal Dose.—Death has resulted from 30 grains being taken by an adult.

Fatal Period.—In six hours after swallowing a piece of “lunar caustic” a child of fifteen months died in convulsions.

Treatment.—Large drafts of common salt and water will favor vomiting and at the same time be the best antidote, forming insoluble silver chlorid. The stomach-pump may be used if necessary. This treatment can be followed up with a diet of eggs and milk.

Postmortem Appearances.—The local action of the caustic will be seen in stains, at first white, and on exposure to light turning black. These stains are found on the lips, in the mouth, on white clothing, and on the mucous membrane of the digestive tract touched by the poison. Gastro-intestinal inflammation is present.

Tests.—*Hydrochloric acid* and *soluble chlorids* precipitate from soluble salts of silver white silver chlorid, insoluble in nitric acid, but readily soluble in ammonia-water.

Potassium iodid gives a yellow precipitate, and *potassium chromate* a blood-red precipitate.

Extraction from Stomach Contents.—Finely divided tissues or gastric contents are digested with ammonia and potassium cyanid. The decanted fluid is treated with excess of hydrochloric acid and the insoluble chlorid separated by decantation; the precipitate is washed on a filter with hot water, dried, and reduced on charcoal to metallic silver.

LEAD

(Chemical Symbol, Pb; Synonym, *Plumbum*.)

The number of deaths from poisoning in England and Wales by lead reported by the Registrar-General for 1883 to 1887 inclusive was 437,³ and in 1894 the number was 132. In the city of New York, from 1870 to 1891 inclusive, 113 cases of accidental death from lead-poisoning were reported by the Board of Health in 1892. Out of 805,412 deaths from all causes registered in the United States for 1910,⁴ 136 were from chronic lead-poisoning. The rate per 100,000 of population was 0.3.

¹ See Brit. Med. Jour., 1887, ii, 321.

² Jour. Amer. Med. Assoc., 1921, 77, 1514.

³ See Taylor, Princ. Med. Jour., 6th ed., 1910, 2, 460; see Section on Industrial Toxicology, p. 774.

⁴ Mortality Statistics U. S. Census for 1910, p. 138.

In spite of this frequency, lead-poisoning rarely figures in the courts, owing to the fact that most of the cases are due to slow absorption of minute quantities, exposure to which is an incident of certain industries dealing with lead or its compounds. The fatal cases given above represent but a small fraction of the persons who in that period, from numberless causes, suffered from degrees of chronic poisoning more or less serious, but not ending in death. That acute lead-poisoning does occur to some extent is shown by the statistics collected in which are recorded 44 deaths in 124 cases, of which 10 were homicidal, 33 non-homicidal, and 1 doubtful.¹

Properties.—Metallic lead dissolves freely in nitric acid, sparingly in strong sulphuric acid when hot, but not in dilute or cold sulphuric acid, nor practically in hydrochloric acid. While not soluble in pure water, the ordinary water served in plumbers' pipes contains enough free oxygen to oxidize a fresh lead surface, which may then form a soluble bicarbonate by the aid of the carbon dioxid present. A portion of it finally forms a crust of insoluble hydrated oxycarbonate, which prevents further action. While silicates,² sulphates, and carbonates tend to prevent the corrosive action of water, nitrites, nitrates, and chlorids increase it; hence a "hard" water-supply is less dangerous when served in lead pipes than a "soft" or purer article. Cowles,³ in the course of years, observed 18 cases occurring in different houses of a rural community using lead pipes. The action of a suspected water may be tested by scraping freshly a piece of lead $2 \times \frac{1}{2}$ inch, and then immersing it in 100 mls (c.c.) of the water for twenty-four hours. If the water should erode the lead there will be turbidity or a sediment. After filtration the clear water may be tested for dissolved lead by the methods given (p. 184).

Lead acetate ($\text{Pb}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 3\text{H}_2\text{O}$) occurs in white masses of acicular crystals. It is soluble in water, and has a taste at first sweetish, hence the popular name, "sugar of lead," but later the taste is styptic and metallic in character. It is present in pharmaceutical preparations as a pill with opium, a compound suppository with opium, and an ointment. The subacetate ($\text{Pb}(\text{C}_2\text{H}_3\text{O}_2)_2$ (PbO), is present in *liquor plumbi subacetatis*, in a dilute form in Goulard's water, and in the compound ointment or Goulard cerate.

Lead Carbonate.—The paint known variously as "white lead," "flake white," and "mineral white" is a mixture of lead hydroxid and neutral lead carbonate. It is present in the official ointment of lead carbonate.

Lead sulphate (PbSO_4), "sublimed white lead." This is a white insoluble powder which is precipitated when a soluble sulphate is given as an antidote in lead-poisoning. It is used to lend weight to white silk and gives the desired body to some brands of white lead paint.

¹ Witthaus, Toxicology, 1911, p. 717.

² Crookes, Odling, and Tidy, Lancet, 1886, ii, 632.

³ Boston Med. and Surg. Jour., 1907, clvii, 325.

Poisonous Salts.—Owing to its dustiness, *lead suboxid* (Pb_2O) causes many cases of plumbism. It forms on the surface of melted lead and vaporizes at the higher temperatures¹ to which it is subjected by lead smelters, zinc smelters, brass molders, and workers in type-metal, lead pipe, wire, solder, and shot. Lead in the cold yields this oxid to the hands.² The higher oxids, *litharge* (PbO) and red lead (Pb_3O_4), are frequent sources of plumbism. The oxids are used for storage-batteries and in making rubber, glass, varnish, pottery glaze, enamel, and paint. The salt which is of most importance in acute poisoning is lead acetate, while chronic poisoning is most frequently caused by lead carbonate.

The subacetate of lead present in Goulard's extract has very much the same effect as the acetate, but greater in degree, as it contains more lead. Lead chromate (chrome yellow), lead oxids (litharge and red lead), and finely divided metallic lead, while not soluble in water, dissolve in the dilute vegetable acids of food and in the gastric juice, and exert a slowly cumulative poisonous action.

"Ledoyen's disinfectant" containing lead nitrate, and "Turner's yellow," or the oxychlorid—in fact all the salts of lead—are poisonous, except perhaps the sulphid and sulphocyanid.³

Acute Lead-poisoning.—*Symptoms.*—At first they are such as result from a local irritant, and are less likely to be fatal from a single large dose than from the same amount taken in fractions at intervals. In a few minutes a metallic taste is perceived, and soon afterward the mouth and throat feel dry and burn. Retching and vomiting may appear in less than half an hour and prove obstinate and persistent. Abdominal pains come on in colicky cramps, relieved by pressure. Usually the bowels are constipated; occasionally the stools are bloody, and at a later date they are dark from lead sulphid. The urine is scanty, the face anxious, the skin dry, the breath fetid, and the tongue coated. While the brain is clear, the involvement of the nervous system is indicated by the headache, the pain and cramps in the legs, and the numbness and local palsies which appear a few hours later. After a few days in some cases a blue line is seen on the gums.

Fatal Dose.—It is not known what single dose of lead acetate would prove fatal. Since recovery has taken place in 3 cases after taking 1 ounce (28.3 gm.) of the acetate, it would seem that the fatal amount must be greater when that salt is the poison. It is probable that the fatal dose of the carbonate would be somewhat less than that of the acetate, though the course of the symptoms would be slower.

Fatal Period.—While death from the acute form is very rare, 23 cases have been collected. It may occur from prostration as early as the second or third day.

Treatment.—The first indication is the washing out of the stomach by a tube or pump, using a solution of magnesium or sodium sulphate.

¹ Hamilton, Jour. Amer. Med. Assoc., 1912, lix, 777.

² See Süssmann, Arch. f. Hyg., 1921, 90, 175.

³ Eulenberg, Gewerbe Hygiene.

In the absence of the tube an emetic dose of alum (a soluble sulphate) would be serviceable. When the stomach is quiet the remainder of the poison can be neutralized and the bowels evacuated by $\frac{1}{2}$ ounce of magnesium sulphate (Epsom salt). The lead sulphate formed must be quickly removed by purging, as it is soluble in the acid gastric juice. To check vomiting and colic the best reliance is on hypodermic injections of morphin and atropin.

Postmortem Appearances.—In the few autopsies which have been held in acute lead-poisoning indications have been found of gastrointestinal inflammation. When life has been prolonged until systemic symptoms appear, mischief has been found in the liver and kidneys.

Chronic Lead-poisoning (Synonyms, *Plumbism*; *Saturnine Intoxication*).—Judging by the cases reported in the medical journals chronic poisoning is of very common occurrence. Gottheil¹ reported plumbism fatal after eight weeks in a patient treated for extensive burns by local applications of dilute Burow's solution of aluminum acetate holding in suspension lead sulphate. In the vast majority the lead enters the body by accident, as a result of its use in certain industries; in a certain proportion it is caused by contamination of food and drink. In these cases the amount of lead in each dose is so small as to escape detection but, owing to its extraordinary cumulative action, in time a sufficient quantity finds lodgment in different organs to produce widespread damage. Out of a total of 1600^{2,3} men employed in white lead industries during sixteen months, 388 cases were found, or 1 case of poisoning in 4 exposed. Andrews' analysis showed that of 60 cases of lead-poisoning in New York, 45 handled paint, 4 were printers, 3 smelters, 3 white lead workers, 2 storage-battery makers, and 1 each in tinning, lead-pipe making, and rubber works. The lead trades are dangerous in proportion to their dustiness, probably some absorption occurs from the bronchial mucosa,⁴ and some because human saliva and the other digestive juices⁵ have a solvent action on the carbonate and other lead salts.

1. *Injurious Industries.*—Operatives in the *metal* are liable to have it introduced by inhalation, by dust-particles getting in the hair, beard, or clothing and indirectly into food and drink, and possibly through the skin, as in the case Shie⁶ refers to that developed from using a cane with a lead head and 2 other mild cases among men who handled pig-lead. When dust is inhaled 70 per cent. is arrested in the nasopharynx and swallowed, while only 12 per cent. reaches the lungs (Lehmann and Saito). In this way many cases have been caused in plumbers, smelters, type-founders, compositors, shot-makers, file-cutters, lead-foil workers, etc. It is even more common in those who work in the lead salts used for colors, such as color-grinders, white- and red-lead makers, japanners,

¹ Jour. Amer. Med. Assoc., 1910, liv, 1056.

² Bulletin 85 U. S. Department of Commerce and Labor, Washington, 1911.

³ Hamilton, Jour. Amer. Med. Assoc., September 7, 1912, lix, 777.

⁴ Oliver in Bulletin 85.

⁵ Carlson and Woelfel, Jour. Amer. Med. Assoc., July 19, 1913, lxi, 181.

⁶ Jour. Amer. Med. Assoc., March 26, 1921, 76, 835.

enamellers, lapidaries, potters, combers of yarn dyed with chrome yellow, and workers on the lead plates of electric accumulators. Shie¹ demonstrated that plumbism may occur from the fumes of molten lead at a temperature of 750° F., which is below the boiling-point. Hamilton² found in Illinois 70 unusual processes involving exposure to lead, to wit: Making and selling wall-paper, polishing brass, polishing nickel, finishing cut-glass, cabinet-making carried on in the same room with the sandpapering of white lead paint; holding lead-covered nails in the mouth while shingling a roof; working with aluminum foil (7 per cent. lead) in lithography; zinc-smelting; making ornamental tiles (with a non-fritted lead glaze); wrapping cigars in tin-foil; enameling bath-tubs; laying electric cables; stopping the inequalities of wood with white lead in making automobiles; assembling and recharging old storage-battery plates³; polishing handles of coffins.

2. *Food Contamination.*—As lead is slightly soluble in water containing certain salts and gases (see p. 176), its wide-spread use for pipes in which beverages are kept standing overnight causes it to be introduced into drinking-water, into ale and beer drawn from the cellar, into seltzer-water kept in siphons. Lead oxid is largely used to make a glaze on pottery. From this it may be dissolved by acid foods, as fruit jellies, pickles, vinegar, lemon juice. As a constituent of solder and the alloy used to tin iron, it finds access to canned goods containing acids.⁴

As a substitute for the yellow of egg in making sweet cakes chrome yellow has been used by bakers, with very grave consequences. In this condition there is a feeling of "poor health," the appetite is small, digestion impaired, energies feeble, and there is more or less profound anemia. An epidemic of lead-poisoning in the north of France, involving over 100 persons, was investigated by Bertrand and Ogier,⁵ who came to the conclusion that the lead was in the flour, obtained by all the sufferers from the same mill, and that contamination came from the elevator buckets, which were "tinned" with lead.

3. *Cosmetics.*—Most of the lotions called "hair-renewers" are preparations containing sulphur and lead acetate or calcium plumbite.⁶ They do not restore the natural pigment, but cause the precipitation of black lead sulphid in the hair structure, so as to simulate the natural color. The use of "flake white" as a cosmetic has caused every form of chronic lead-poisoning.

4. *Lead Shot in the Tissues.*—A bullet embedded in the flesh may in time cause systemic poisoning, especially anemia, but bird-shot presenting a great surface for absorption sometimes acts in a brief period. A case is reported⁷ of a healthy boy of fifteen years, who re-

¹ Jour. Amer. Med. Assoc., 1921, 76, 835.

² Ibid., 1911, 56, 1241.

³ See Heim, Lafont, and Feil, Presse méd., 1922, 30, 92.

⁴ Wightwick, Lancet, 1888, ii, 1121.

⁵ Brit. Med. Jour., 1887, ii, 1228.

⁶ Chandler, New York Board of Health, 1870.

⁷ Curtillet and Lombard, Lyon Chirurgical, 1912, vii, 393.

ceived and retained in his forearm lengthwise, a full charge from a shotgun. In twelve days the local swelling subsided, but severe symptoms of plumbism developed, fatal in twenty-five days. Waxy complexion, headache, insomnia, vertigo, and anorexia were the main symptoms. Nine similar cases are on record, all characterized by early and profound anemia.

Lewin,¹ having studied a large number of cases from shot swallowed or embedded in tissues, favors extraction without delay to obviate the liability to insidious harm. The chemical action of the organic fluids may mobilize the lead at any time with results that are uncontrollable.

Symptoms of Chronic Lead-poisoning.—The classic clinical picture includes anemia, anorexia, a blue line on the gums, local paralysis, especially of the right forearm, lead in the urine, colic with constipation, joint pains, and disorders of the central nervous system, but no one of these is essential to the diagnosis. Basophilic granules in the red blood-cells may be present in 50 per cent. of the cases, but their diagnostic significance has been exaggerated (Vaughan, Linenthal,² Oliver).

The following typical cases were reported by the writer.³ A seamstress, aged twenty-eight years, had been using "flake white" as a cosmetic applied freely for more than two years to the face to conceal freckles. Within two years her skin had become dry, pale, and sallow, her conjunctivæ yellow, her hair had fallen out, she had dyspepsia, debility, and low spirits. She had repeatedly suffered from constipation and colic attributed to indigestion. Headache and vertigo had been at one time an every-day experience, and after a year of minor symptoms she went under treatment for melancholia, the cause being at that time undetermined. While confined she left off the cosmetic, but after a month of tonics her mind was restored and she resumed the pernicious habit. One month before she came under observation her hands had become weak and tremulous, her spirits depressed and irritable, and a double wrist-drop had developed. The extensors of the forearms and interossei muscles of both hands were completely paralyzed, the flexors were slightly affected, and the supinators apparently unharmed. There was characteristic loss of electrocontractility to faradism, though slowly interrupted galvanism elicited some response. The gums had a blue line, the lead cachexia was marked, and the cosmetic had been spread thickly to redeem the ravages made by itself. Her younger sister was seen later suffering from wrist-drop, with blue line on the gums, cachexia, with a history of frequent attacks of pain in the elbow and shoulder, with convulsive seizures that had been treated as epileptic. Lead was present in the urine of both.⁴

The site of the lead palsy depends upon what nerves and muscles are most used and most liable to be overworked. This turns upon the

¹ Archiv f. klin. Chirurgie, Berlin, 1910-11, xciv, 937.

² Jour. Amer. Med. Assoc., 1914, lxii, 1796.

³ Report of Kentucky Board of Health, 1881.

⁴ See also Robinson, Jour. Amer. Med. Assoc., 1915, lxiv, 814.

requirements of the occupation. Seamstresses, painters, and printers have palsy of the right forearm and hand. File-cutters are affected in the left hand which holds the chisel. Using their legs more than arms children show leg-weakness. Ordinary laborers lose strength in both arms and legs.

The relative frequency of the different symptoms was shown in the Philadelphia cases reported by Stewart. They were caused by eating cakes made yellow with lead chromate.¹ Most of the 64 cases exhibited the ordinary signs of impaired nutrition with the characteristic cachexia. They had the colic with constipation, the joint-pains mistaken for rheumatism, and the blue line on the gums caused by the reaction between lead albuminate in the gum and hydrogen sulphid of decomposed food-particles between the teeth. Lead was found in the urine of all cases examined. All the cases whose history covered several months were emaciated. Well-marked lead cachexia was present in 78.21 per cent., and the remainder were all more or less sallow. There was frequent vomiting in 79.68 per cent. Some colic was experienced by 76.56 per cent., and the peculiar rotating umbilical lead colic in 60.93 per cent. In 73.43 per cent. there were joint-pains, growing worse at night and not inflammatory in character. The parts affected most often and most severely were the flexor surfaces of the knees and ankles. Bilateral wrist-drop from paralysis of the extensors of the forearm occurred in only 2 cases. Minor degrees of nervous and muscular disorder in the forearm occurred in 3 other cases. The most serious symptoms were those involving the brain and spinal cord. Headache, so constant and severe as to indicate deep cranial mischief, was present in 73.47 per cent. Brain disease was present in 23.43 per cent., causing epileptiform convulsions in 17.18 per cent., delirium in 3.12 per cent., melancholic mania in 1, and coma in 1. The blue line on the gums was shown by 89 per cent., and probably by 6 out of the 7 remaining. The mortality was 12.5 per cent. Postmortem examination of the viscera was made in 5 cases, and revealed lead in all. Reese found it in the brain and spinal cord five months after death.

The fatal cases were characterized by eclampsia due to encephalopathy. It has been suggested that the gravity of the nervous phenomena was doubtless due in some degree to the chromium present in the poison.

Lead appears to form some stable combination with the substance of the nervous system, and induce thereby disturbed function, if not local destruction, of some essential part of the great centers, as well as of the peripheral nerves. There is elevation of the blood-pressure, the red blood-cells have basophilic granules, and leukocytosis exists. Billings² noted the fact of disease of the blood-vessels caused by lead either directly or indirectly. In the train of arteriosclerosis he found gout, the contracted kidney, and left cardiac hypertrophy. The sclerotic blood-vessels of the brain cause central cerebral changes characterized by epileptic attacks, hallucinations, and other mental

¹ Medical News, 1887, 1, 676; see also *Ibid.*, 1889, liv, 85.

² Jour. Amer. Med. Assoc., 1904, xliii, 772.

disorders. In a case of fatal lead-poisoning examined by Blyth the cerebrum was found to contain lead equivalent to $1\frac{1}{2}$ grains of sulphate, and the cerebellum about $\frac{1}{4}$ grain. An optical neuritis may cause visual disturbances, but these are sometimes due to the retinitis secondary to the kidney mischief. The germ-cells of the male parent subject of plumbism are detrimental to the offspring. Paul¹ reported 32 such pregnancies, of which 12 had premature fetal death, and of the 20 delivered alive only 2 survived the third year. By experimental breeding with male rabbits and fowls poisoned with lead acetate, Cole and Bachhuber² proved that such progeny was subnormal in vitality and weight.

Treatment of Chronic Poisoning.—By careful inquiry the source of the lead may be discovered, and the patient should be guarded against further exposure to it. In the case of operatives in lead-works, emphasis must be laid upon the necessity of grinding the pigments under water to prevent the fine particles escaping as dust into the air; free ventilation is requisite; the hands, nails, and beard should be washed and brushed carefully before eating, and meals should not be taken inside the factory. A weak lemonade of sulphuric acid is sometimes used as a beverage. Its value is seriously questioned since it has been shown by Carlson and Woelfel³ that lead sulphate is soluble in the gastric juice. A glass of milk between meals is useful to prevent this solution of lead salts in the free hydrochloric acid of the stomach. In some works the men have a habit of taking a laxative dose of magnesium sulphate several times a week. This precipitates the lead in a less active form and expels it in the feces.

Every worker who incurs the lead hazard should be inspected periodically, and at the first sign of plumbism a change in occupation should be advised. The workers should be enjoined that every detail of personal hygiene must be observed if lead absorption is to be prevented.

It is well to begin treatment with a dose of Epsom salt as an antidote to any lead present in the alimentary tract; colic will call for morphin and atropin administered hypodermically; joint-pains for local fomentations; paralysis for electricity and massage. The natural process of elimination of lead is deliberate. The investigations of Mann⁴ show that it escapes slowly by the urine, and five to ten times as much by the bowels, without the use of any special eliminant. Several special eliminants, notably potassium iodid, were given freely without causing any increase in the amount of lead excreted. Careful quantitative tests proved that a slight increase attended the use of hot baths, general massage, and occasional purgation. These last, combined with open-air exercise and wholesome diet, are the means most to be relied on. If potassium iodid is given, care should be taken that it

¹ Osler's Modern Med., 1907, 1, 44.

² Proc. Soc. Exper. Biol. and Med., 1914, xii, 24; also Weller, Jour. Med. Research, 1915, 33, 27.

³ Jour. Amer. Med. Assoc., 1913, 61, 184.

⁴ Brit. Med. Jour., 1893, i, 401.

does not increase the anemia. A remission should be allowed during which iron preparations would be of service.

Prognosis.—If seen early and toxic exposure be stopped at once, the prospect of recovery is good even in wrist-drop. If it be uncomplicated with the effects of alcohol or the degenerations of liver, kidney, heart, and blood-vessels, plumbism does not progress further. Some disability may persist if muscular atrophy has supervened upon local palsy, or if marked mental derangement be the sequel to cerebral symptoms.

Postmortem Appearances.—In chronic cases the pathologic changes discovered cannot be called characteristic. Where albuminuria has been present, the kidneys are found hard and contracted, the seat of granular degeneration. When colic has been a conspicuous symptom, a portion of the intestines has been found constricted, with a gray-black discoloration of the mucous lining. When there has been local paralysis with atrophy, the muscles involved have been found wasted and fatty, and changes have been discovered in the large cells in the anterior cornua of the cord and in the peripheral nerve-fibers. The blue line around the gums is highly significant.

Distribution and Elimination.—In examining the bodies of 2 cases suddenly fatal, Blyth¹ separated from the brain of one an appreciable amount of lead, from the liver an amount equivalent to $\frac{1}{3}$ grain of sulphate, from one kidney about $\frac{1}{13}$ grain. Heubel found in a dog killed by chronic lead-poisoning, in parts per thousand—the bones to contain 0.18 to 0.27; the kidneys, 0.17 to 0.20; liver, 0.10 to 0.33; spinal cord, 0.06 to 0.11; brain, 0.04 to 0.05; muscles, 0.02 to 0.04; intestines, 0.01 to 0.02, and traces were detected in the spleen, blood, and bile.

It is a remarkable fact that lead is frequently found in persons apparently healthy—certainly free from all symptoms of lead-poisoning. A fallacious conclusion may be reached if the contents of the stomach should contain a bit of melted solder from a fruit-can or a shot derived from eating game. Bedson found traces of lead in the urine of all of 23 leadworkers that seemed to be well. Oliver² calls this "latent" plumbism.

In the absence of characteristic symptoms during life, if the amount of lead separated from the tissues should be small, it should not be regarded as significant of lead-poisoning.

Elimination is by the urine, the bile, and the intestines, the fecal content exceeding that of the urine even when the lead enters by some other portal than the mouth. The retention of lead in the body is not uniform owing to conditions, not well understood. In some cases of plumbism the urine is lead-free for months, and then without additional administration it again shows the metal.

Lead in the Urine.—From a case reported by Dercum³ which had

* ¹ Lancet, 1887, i, 1053.

² Bull. U. S. Dept. Commerce and Labor, Ind. Lead Pois., 1912.

³ Medical News, 1887, i, 4.

symptoms so vague as to make the diagnosis of lead-poisoning doubtful, Marshall obtained from 400 c.c. (14 fl. oz.) of urine as much as 5.2 mg. (0.08 gr.) of metallic lead.

There is reason to believe that lead is not an uncommon constituent of the urine. Putnam¹ made 86 urine analyses for lead in the healthy and the sick, with the result of finding lead present in 48 cases. He made allowance for the fact that most of them were chosen because of their exposure to lead by occupation or otherwise, and concluded that so far as his figures are a guide, in not more than 50 per cent. of the community at large can lead be detected in the urine. He noted that the urines of persons known to be in perfect health were almost all free from lead.

Tests.—1. *Hydrogen Sulphid.*—A stream of this gas passed through a lead solution, neutral, alkaline, or slightly acid, yields a black precipitate of lead sulphid, insoluble in the alkaline hydroxids or the moderately dilute acids. If the amount of metal be very small the precipitate will be brown. Hot nitric acid converts it into soluble lead nitrate, and free sulphur separates; by continued heat the acid converts the sulphur into sulphuric acid, and this precipitates the lead as lead sulphate. A small amount of lead would remain in solution.

Fallacies.—This reagent gives a like precipitate with several other metals, such as copper and mercury. To distinguish the lead, the sulphid may be dissolved in warm dilute nitric acid, filtered, the filtrate evaporated to dryness to expel any excess of nitric acid, the residue taken up with water, and the clear solution tested, as stated below, with potassium iodid, dilute sulphuric acid, or potassium chromate. If the quantity of the precipitate is large, it can be reduced to metallic lead by the blowpipe or charcoal.

Delicacy.—From a solution containing $\frac{1}{25000}$ grain of lead oxid to 10 grains of water Wormley² got a faint brownish tint with perceptible cloudiness.

2. *Potassium Iodid.*—This reagent gives, with very small amounts of lead, a yellow coloration; with larger amounts, a yellow precipitate of lead iodid soluble in boiling water, from which it deposits on cooling in gold-colored hexagonal scales.

Fallacies.—If the lead is small in amount and has been treated previously with nitric acid, a brownish color will be caused by the iodine freed from the potassium, unless the free nitric acid has been neutralized or driven off by heat. Lead iodid is soluble in potassium hydroxid and in strong hydrochloric acid.

Delicacy.—Wormley³ states that a very small quantity of the reagent will cause a satisfactory deposit of small plates from a solution of $\frac{1}{20000}$ grain.

3. *Sulphuric Acid.*—This reagent diluted gives a white crystalline or granular precipitate of lead sulphate, which is favored by the

¹ Trans. Assoc. Amer. Phys., 1887, ii, 235.

² Wormley, Micro-Chemistry of Poisons, 1885, p. 371.

³ Wormley, Ibid., 1885, p. 375.

addition of alcohol. The precipitate is soluble in hot strong hydrochloric acid, in ammonium acetate, and in a large excess of potassium hydroxid.

Fallacies.—This reagent will also make a white precipitate with barium and strontium salts, and with fairly strong solutions of calcium compounds. The lead sulphate is characterized, however, by turning black with ammonium sulphid.

4. *Potassium Chromate or Bichromate.*—Either of these reagents precipitates lead as a yellow amorphous deposit soluble in potassium hydroxid and strong hydrochloric acid, but insoluble in acetic acid. A yellowish precipitate produced by potassium chromate in neutral copper solutions dissolves in acetic acid, and is thus readily distinguished from the lead precipitate.

Detection in Gastric Contents, Tissues, etc.—A method suitable for the urine, feces, gastric contents, or the finely divided viscera is the evaporation of the fluid or the dilution of the solids to the consistence of a gruel, the destruction of organic matter with potassium chlorate and hydrochloric acid (see p. 46), and filtration while hot. While some of the lead is apt to remain as insoluble sulphate on the filter, a considerable quantity in a soluble combination with potassium chlorid passes through. In toxicologic analysis, as a rule, the total amount of lead is not in excess of what will be dissolved. The filtrate may be precipitated with hydrogen sulphid, the precipitate dissolved in warm dilute nitric acid, the solution filtered and evaporated to dryness, the residue redissolved in water, and tested with sulphuric acid or potassium iodid.

Detection in Urine.—The following method for the urine, devised in its present form by E. S. Wood,¹ is very delicate. A quart of urine acidified with acetic acid is evaporated to dryness and fused in a crucible with a little pure niter until it becomes white. When the crucible is cool, dilute hydrochloric acid is added *hot* to extract the residue after ignition. The extract is then filtered and the filtrate treated with ammonia to alkaline reaction, to precipitate the phosphates and iron. Ammonium sulphid is added at the same time to throw down the lead and iron as sulphids. This deposit is washed three times by decantation with hot water; then water acidified with hydrochloric acid is added, and the whole allowed to stand until the next day. It is then filtered through a small filter and the residue washed. A little pure nitric acid is then added drop by drop to dissolve the lead sulphid left on the filter and carry it through as nitrate. This filtrate is collected in a watch-glass, evaporated to dryness, and the final test made by adding a drop of water and a crystal of potassium iodid. A yellow precipitate denotes lead.

Electrolysis.—To electrolyze the filtrate of the hot decoction with potassium chlorate and hydrochloric acid, it is placed in a glass vessel, with a bottom of parchment-paper. This cell is immersed to the surface level in an outer vessel containing distilled water acidulated with sulphuric acid. In the inner cell is placed the cathode of four Grove's

¹ Putnam, Trans. Assoc. Amer. Phys., 1887, ii, 235.

cells in the shape of platinum foil 50 cm. square (2×4 in.). Beneath the parchment diaphragm, near to it and parallel with the cathode on the opposite side, is placed the anode. In six hours the cathode is removed, washed, dried, and cleaned of its lead with warm dilute nitric acid. After driving off the free nitric acid by heat the lead is precipitated by dilute sulphuric acid and an equal volume of alcohol added. After being set aside for twenty hours, the precipitate is washed free from acid with water containing 12 per cent. of alcohol. Decanted, ignited, and weighed, 100 parts of the sulphate equal 68.319 parts of metallic lead.¹

Quantitative Determination.—While the electrolytic method is preferable when the amount of lead is small, for large quantities it is better to precipitate the lead dissolved by decoction in hot hydrochloric acid with hydrogen sulphid. The precipitate may be converted into sulphate by treating it first with warm dilute nitric acid, filtrating, evaporating, dissolving in water, and precipitating with sulphuric acid, evaporating, igniting, and weighing as above, calculating 68.319 parts of lead for 100 of the sulphate.

MERCURY

(Chemical Symbol, Hg; Synonyms, *Quicksilver*: *Hydrargyrum*.)

This is a liquid which changes to vapor spontaneously at all temperatures above 41° F. (5° C.). If finely triturated, the globules remain separate if the trituration has been done in the presence of some substance which gives a coating, such as fatty matter or a confection.

The metal has been given in the pure state to remove obstruction from the bowels mechanically, with no injurious consequences unless retained for a number of days. Taylor² cites a case in which, after retention for nine days, some salivation was produced, all the metal not being expelled until the fourteenth day. The metal is present finely divided and possibly oxidized in gray powder (*Hydrargyrum cum Creta*, U. S. P.), blue-mass (*Massa Hydrargyri*, U. S. P.), blue ointment (*Unguentum Hydrargyri*, U. S. P.). In this condition, and also if inhaled in the state of vapor, the metal is converted by the fluids of the body into active compounds which exhibit all its poisonous effects. Among its poisonous salts are the black mercurous oxid, the red mercuric oxid (red precipitate, yellow precipitate), the yellow mercurous iodid, the red mercuric iodid, mercurammonium chlorid (white precipitate), mercuric nitrate (acid nitrate of mercury), mercuric chlorid (corrosive sublimate).

Calomel (*Mercurous Chlorid*, HgCl).—A heavy, white, insoluble, tasteless powder that is not considered poisonous. If retained, however, it changes to some more active compound, such as the poisonous mercuric chlorid, and then produces systemic symptoms. It is so extensively used that milder toxic effects are not infrequent, owing to these changes in the stomach or in the prescription due to incompatible association.

¹ See Schumm, *Ztschr. f. physiol. chem.*, 1922, 118, 189.

² Taylor, A. S., *On Poisons*, 1875, p. 351.

It is probable that most of the few fatal cases reported were brought about by the conversion of the calomel by the fluids of the body into some poisonous salt. One fatal case is reported by Runeberg,¹ in which three hypodermic injections of calomel of $1\frac{1}{2}$ grains each were given in one month. Collapse supervened upon salivation and diarrhea. It is converted into mercuric chlorid by nitrohydrochloric acid and chlorin water, and probably to a slight extent also by hydrochloric acid and alkaline chlorids. It is changed to oxid or reduced by the alkaline bases and carbonates. Prolonged exposure to sunlight changes it to metallic mercury and mercuric chlorid.

Corrosive sublimate (HgCl_2 ; *Mercuric chlorid*) is usually seen in crystalline masses; it sublimes at 180° F. (82.2° C.), and is deposited

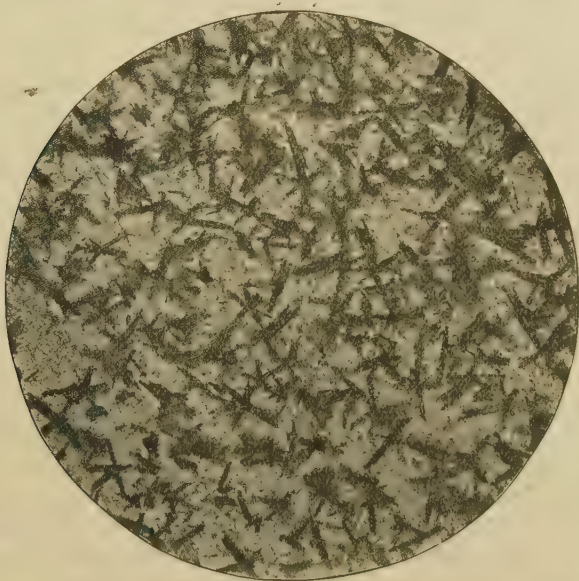


FIG. 29.—Sublimate of mercuric chlorid magnified. Stellate crystals.

in needles, in octahedra, or in stellate aggregations of crystalline plates (Fig. 29). It has no odor, but an acrid, metallic taste. It is soluble in 16 parts of cold water and 3 parts of boiling water, but is far more in solutions of common salt or other alkaline chlorids. It is freely soluble in alcohol and ether, makes a definite insoluble compound with protein matter, such as albumin, and is fatal to low forms of animal and vegetable life. A solution of it is used in the household to destroy bed-bugs, and by taxidermists to preserve skins and mounted preparations. In antiseptic surgery it is extensively employed as a bactericide in irrigating solutions of 1 : 4000 or even 1 : 1000 of water. Its vogue in

¹ Deutsch. med. Wchnschr., 1889, xv, 4. Backer (Hospitalstid., 1921, 64, 737) reports a case of fatal poisoning following the intramuscular injection of 1 c.c. of a 10 per cent. suspension of calomel, death resulting one week after the third injection.

surgery began about 1880, and its frequency as a poison increased at the same time. Of 559 cases mentioned in medical literature from 1800 to 1910, 422 have been since 1879.¹ Of these, 24 occurred in the decade 1870 to 1879, and during 1880 to 1889 there were 152. Of the 422 after 1879, 179 were due to irrigations of vagina and uterus, and 66 were fatal. In some death followed surgical operations in which antiseptic irrigation was practised. After the usual symptoms of mercurial poisoning the postmortem appearances attending such poisoning were also discovered. Of 312 cases other than obstetrical and surgical 132 were accidental, 126 suicidal, and 29 homicidal. Under the official U. S. P. (IX) title, *Toxitaellæ Hydrargyri Chloridi Corrosivi* (Poison Tablets of Corrosive Mercuric Chlorid), it is dispensed in a blue colored, angular form, stamped POISON, each tablet weighing about 1 gram and containing about 0.5 gram each of corrosive sublimate and common salt.

Fatal poisoning has occurred from swallowing by mistake a tablet of corrosive sublimate for one of phenacetin, and also from the introduction of a tablet into the vagina² for the purpose of preventing conception or inducing abortion. Owing to the ease with which the sublimate tablets can be bought in this country, and the fact that some of those ordered uncolored for surgical antisepsis were often left over for the medicine closet, such cases are more frequent with us than in Germany, where rigid laws prevail for their sale and for making up the packages containing them. In the German Empire during 1897 to 1905³ only 101 cases were reported of poisoning from sublimate tablets, and 23 from sublimate in powder. Of the 101 tablet cases, 92 were suicidal, and 9 accidental; none were homicidal and none per vaginam. The recoveries numbered 43, fatalities 58. Of the 23 sublimate powder cases, 16 were suicidal by intention, and 6 accidental, including 2 fatalities due to vaginal injection to prevent conception.

Symptoms of Acute Poisoning from Corrosive Sublimate.—This salt, however administered, is a very active gastro-intestinal irritant. When taken by the mouth, the symptoms usually begin within a few minutes. The onset is rarely delayed half an hour, but Wood⁴ reported a case in which symptoms were delayed one and a half hours. They are an acrid, metallic taste, constriction of the throat, retching, and a burning sensation in the gullet and stomach. A white coating forms at once on the shriveled lining of the mouth, the inflammation of the throat may involve the larynx, and acute swelling of the glottis may cause asphyxia. The pain in the stomach is so severe as to cause fainting. It comes on promptly, attended by nausea and vomiting of material streaked with blood, and later on purging and straining with bloody stools. Free

¹ Witthaus' Toxicology, 1911, p. 731. See also Sayers, Bureau Mines Repts., Investigations No. 2354, 1922; Guillain and Gardin, Ann. de Med., 1922, ii, 338.

² Lankford, Jour. Amer. Med. Assoc., 1910, liv, 1203; Sharp, Ibid., 1910, liv, 1458; Patik, Ibid., 1910, liv, 1867; Bland, Ibid., 1920, lxxiv, 1227. Frederick, Can. Med. Assoc. Jour., 1920, x, 751; Sexton, Jour. Amer. Med. Assoc., 1922, lxxviii, 1445.

³ Franz, Arb. a. d. k. Gsndhsamte, 1910, xxxiv, 1.

⁴ Jour. Amer. Med. Assoc., 1915, lxiv, 507.

hemorrhages occur from stomach, bowels, or other outlet. The urine is scanty or suppressed, the temperature may be febrile or subnormal, the respiration difficult, the pulse thready and irregular. Death is preceded by collapse, unconsciousness, or convulsions. A typical case was reported by Church¹: A child, aged three years, by mistake was given a dose equal to $10\frac{3}{4}$ grains of corrosive sublimate; it immediately caused bloody vomiting, soon followed by intense thirst, drowsiness, weak and rapid pulse, temperature 105.6° F., dilated pupils, and twitching of eyelids. The urine was suppressed, the bowels occasionally moved, with discharges of bloody mucus. There was no salivation, but profuse mucous discharge from the nose. Death occurred in twenty-two hours. Durante² has reported the case of a woman, aged twenty-five years, who took a large teaspoonful of corrosive sublimate in powder. She vomited, had burning pain in the throat, active diarrhea, suppressed urine, physical depression, stupor, swollen tongue and lips, dysphagia, colic, and abdominal tenderness, followed by death in ten days.

Fatal results have followed the application of an alcoholic solution of corrosive sublimate (80 gr. to the ounce) to the scalp for ring-worm. Anderseck³ records 2 fatal cases poisoned by the external application of an ointment of corrosive sublimate to cure the itch. In these cases, besides the painful local inflammation, in a few days gastro-intestinal symptoms appeared, such as vomiting and purging with tenesmus. In addition there were stomatitis, fetid breath, fever, scanty urine, and collapse. Sackur⁴ has reported a case of fatal acute poisoning from rubbing a small amount of mercurial ointment into cracks of the skin of the hand for a local lymphangitis. In an hour the patient was seized with faintness and vomiting, and on the next day with tenesmus and albuminuria. The later symptoms were continued vomiting, hematemesis, diarrhea with stools of blood, anuria, salivation with gangrenous glossitis and gingivitis, paralysis of the extremities, and death on the sixth day. The lesions were found to be characteristic of mercurial poisoning—*i. e.*, erosions of the small intestine with changes in the large intestine, such as attend severe dysentery and necrotic degeneration of the epithelium in the renal tubules. When the poison is absorbed as a result of irrigation of wounds of the vagina, uterus, or abscess cavities, Butte⁵ has found the digestive organs profoundly affected. An earlier effect was serous diarrhea, which afterward became bloody, attended by colic and tenesmus, nausea, and vomiting. He usually found the urine albuminous, containing epithelial cells and granular casts. While there might be severe headache, insomnia, dimness of vision, and transient disturbance of the intellect, the mind was usually clear to the end. The pulse grew weaker, the pupils contracted, the temperature fell, and sometimes an intense erythema appeared.

¹ Edinb. Med. Jour., 1887, xxxii, 795.

² Bull. de la Soc. anat., 1892, lxvii, 548.

³ Blyth, A. W., Poisons, Effects and Detection, 4th ed., 1906, 676.

⁴ Berl. klin. Wochenschr., 1892, xxix, 618.

⁵ Brit. Med. Jour., 1887, i, 175; C. R. Soc. de Biol., 1886, 8 S., iii, 491; Ann. d. Hyg., 1887, 3 S., xvii, 167.

The great frequency of deaths from antiseptic irrigations with corrosive sublimate led Fleischmann¹ to plead for its disuse in obstetric practice. He reported a case in which two vaginal injections were given at the time of examination, the second of which was soon followed by severe abdominal pain, serous diarrhea, and vomiting of bile. The woman was delivered without difficulty, but died in six days after showing characteristic symptoms of mercurial poisoning. The autopsy revealed spongy gums, ulcers of tongue, pharynx, and ascending colon, with acute parenchymatous nephritis.²

Fatal Dose.—It is probable that fatal consequences would follow doses of 3 to 5 grains³ of corrosive sublimate. The minimal uniformly lethal intravenous dose, without anuria, was found by Sansum⁴ to be 4 mg. per kilo, while 5 mg. per kilo produced anuria before death. For a man weighing 70 kilo (150 pounds) those figures would be about 4 and 5 grains respectively. Recovery has resulted after the administration of 100 grains under prompt treatment by milk, eggs, and emetics. *White precipitate* or mercurammonium chlorid was at one time regarded as non-poisonous. Several deaths from it have been reported—one from 35 grains.⁵ *Red precipitate* has caused acute gastro-intestinal irritation when given in doses of 2 or more drams. *Acid mercuric nitrate*, intended to be used externally only as an escharotic, has been followed by death after such use, and also when administered internally. The *yellow subsulphate*, or turpeth mineral, used in the treatment of croup, has often caused alarming symptoms. Two doses of 3 grains each have been sufficient to cause death.⁶

Fatal Period.—Death may occur in half an hour from shock, but commonly life is prolonged for two to four days, and it may last into the second week.

Treatment.—Give at once several raw eggs in a quart of milk, and evacuate the stomach with tube or emetic if necessary. Follow this with Linhart's⁷ antidote, which consists of sodium phosphite suspended

¹ Centralbl. f. Gyn., 1886, x, 761.

² For further study the following cases have been taken from the Jour. Amer. Med. Assoc. Fitzgibbon, G.: Poisoning from Mercury Tablet Introduced in Vagina, Lancet, March 16, 1918; abstr. Dublin J. M. Soc., April, 1918. Conaway, W. P.: Fatal Case of Mercury Poisoning from Vaginal Absorption, J. M. Soc., New Jersey, March, 1917. Buckman, F.: Case of Mercuric Chlorid Poisoning Due to Vaginal Douches, The Journal, February 14, 1914, lxii, p. 535. Baux, G., and Roques, E.: Fatal Mercurial Poisoning from Intra-uterine Injection, Rev. mens. de gynéc., d'obstét. et de pédiat., January, 1912; Obstétrique, March 9, 1912, p. 740. Mabbott, J. M.: Mercuric Chlorid Poisoning, Associated with Secondary Hemorrhage from Vaginal Douche, Given Seven Days After Delivery, The Journal, August 15, 1911, lvii, p. 448. Lankford, Burnley: A Peculiar Case of Mercurial Poisoning, The Journal, April 9, 1910, liv, p. 1203. Shrap, W. H.: The Careless and Criminal Use of the Mercuric Chlorid Tablet, The Journal, April 30, 1910, liv, p. 1459. Patek, Arthur J.: Poisoning by Mercuric Chlorid Through Vaginal Douches, The Journal, June 4, 1910, liv, p. 1867. McPeck: Jour. Amer. Med. Assoc., 1920, lxxv, 672. Bland, *ibid.*, 1920, lxxiv, p. 1227.

³ A. S. Taylor, On Poisons, 1875, p. 367.

⁴ Sansum, Jour. Amer. Med. Assoc., March 23, 1918, lxx, 825.

⁵ J. D. Mann, Forensic Medicine and Toxicology, Philadelphia, 1893, p. 448.

⁶ "Medicus," Med. and Surg. Rep., 1884, l, 93.

⁷ New York Med. Jour., 1913, xcvi, 1236; Jour. Lab. and Clin. Med., 1917, ii, 722.

in water at room temperature, and treated with a saturated solution of sodium bicarbonate until effervescence ceases and the solution is perfectly clear. To prepare the pure sodium phosphite Linhart advises the use of 1 part of stick phosphorous acid and 4 parts of sodium bicarbonate dissolved in sufficient water to make a 10-per-cent. solution. Instead of the above one may use Carter's¹ antidote, either in powder or tablet form. This is a modification of the Linhart antidote, and consists of 6 grains (0.4 gm.) sodium phosphite and 4 grains (0.25 gm.) sodium acetate. If this be not at hand employ the antidote of Fantus'²—i. e., sodium hypophosphite, 1 gram; water, 10 mls (c.c.); hydrogen peroxid, 5 mls (c.c.), every eight hours for two days until ten times as much sodium phosphite or hypophosphite has been given as of the suspected poison. Repeated gastric and colonic washings with these antidotes diluted are needed to reduce the mercuric chlorid to the mild mercurous form (calomel) until the mercury disappears from the washings and the urine. For three weeks or until recovery the diet should consist mainly of milk, raw eggs, and carbohydrates.

Good results have been claimed for the method of Lambert and Patterson,^{3, 4, 5} the essentials of which are repeated doses of milk alternated by stomach and colonic washings, using diuretic solutions of potassium bitartrate and sugar. Daily sweats assist the eliminants. The addition of a continuous rectal drip of potassium acetate, while of value in protecting the colon, makes the technic difficult outside a hospital. Confidence has been much impaired in this use of strong diuretics to relieve the swollen kidney and prevent anuria, owing to the studies of Sansum,⁶ which emphasize the uselessness of all such therapeutic measures to save life in cases where a dose of 4 grains has been absorbed. He found that the life of poisoned animals was shortened by copious systemic flushing in principle equivalent to the diuretic courses referred to.

Postmortem Appearances (see Plate 1).—Some parts of the alimentary canal are sure to show inflammatory change. In the mouth, throat, and stomach there will be patches of congestion and erosion, or the intestines, especially the colon, may be the seat of inflammation. Eventually the kidneys swell and take on acute inflammation. In Church's case, cited above, the autopsy revealed whiteness of the gums; a band of intense congestion 3 inches wide along the lesser curvature of the stomach; duodenum normal; mucous membrane of the small intestine of a grayish color, in the lower part greenish; and in the sigmoid flexure was a patch of congestion about the size of a florin. In Durante's case, cited above, the autopsy showed enlarged liver with subcapsular effusions; subpericardial ecchymoses; pale swollen kidneys with small effusions in the pelves; the esophagus red in the upper part; the stomach

¹ Chicago Med. Recorder, 1914, xxxvi, 444; Critic and Guide, 1915, 266.

² Jour. Lab. and Clin. Med., 1916, i, 879; 1917, ii, 813.

³ Arch. Int. Med., November, 1915, xvi, 865.

⁴ Weiss, Jour. Amer. Med. Assoc., June 2, 1917, lxviii, 1618.

⁵ Brown and Baskett, Ibid., p. 1422.

⁶ Jour. Amer. Med. Assoc., March 23, 1918, lxx, 824.

contained patches of effusion and of softening, with large ulcerations, and the intestines were deep red in limited areas, with ulcers; the brain showed injection of the meningeal vessels. According to Burmeister and McNally,¹ within a very few minutes after administration mercury can be detected in the blood and degenerative changes occur in the kidney. The immediate renal changes vary with the size of the dose if it be massive, while hepatic changes vary as the duration of the intoxication.²

When death has occurred from absorption of the poison as a result of application to the skin or irrigation of abscesses or of wounds, or of the uterus and vagina, the most important lesions are in the digestive tract. Butte, as cited above, found the inflammation generally limited to the colon. There is hyperemia of the mucous membrane, with easy detachment of the epithelium, patches of superficial necrosis in some parts, and in others a diphtheric coating infiltrating the deeper layers. The kidneys show a characteristic acute parenchymatous nephritis. In some cases the peritoneum is slightly injected. The liver shows no marked lesion, but is generally pale and anemic.³ The other organs may be unaffected.

Chronic Poisoning or Mercurialism.—The conclusion of Wile and Elliott⁴ was that non-volatile salts of mercury annointed are absorbed through the skin, while inunctions of volatile salts act by volatilization and inhalation. No matter what the mode of entrance, the experiments of Lieb and Goodwin⁵ prove the excretion of mercury by the gastric mucous membrane. The cycle of absorption, excretion, and reabsorption accounts for the persistent systemic action and delay in the final exit of the poison. It also justifies the prolonged egg dosing and gastric lavage recommended in acute poisoning.

The operatives in quicksilver mines, mirror-makers, fine gilders, thermometer- and barometer-makers,⁶ workers of mercury vacuum pumps for electric bulbs, furriers, and hatters are liable to a chronic disease ending in paralysis, brought about by the daily introduction and accumulation in the system of minute doses of mercury probably inhaled as vapor or absorbed by the skin.⁷ Munition workers making mercury fulminate for detonators suffered dermatitis and inflammations of conjunctiva, nasal, and laryngeal mucosa. Some of the milder symptoms have been induced by the incautious use of mercurials in the treatment of secondary syphilis, and by repeated applications to the skin of a weak lotion of corrosive sublimate for cosmetic purposes. Schulte⁸ found mercury in the urine of all of 10 dentists

¹ Jour. Med. Research, March, 1917, xxxi, 1. See also Mentin, Jour. Med. Res., 1922, 43, 315.

² See also Schieck, Deutsch. Arch. f. klin. Med., 1920, cxxxiii, 99.

³ See, however, Turrettini and Piotrowski, Rev. Méd. de la Suisse Rom., 1921, 41, 178.

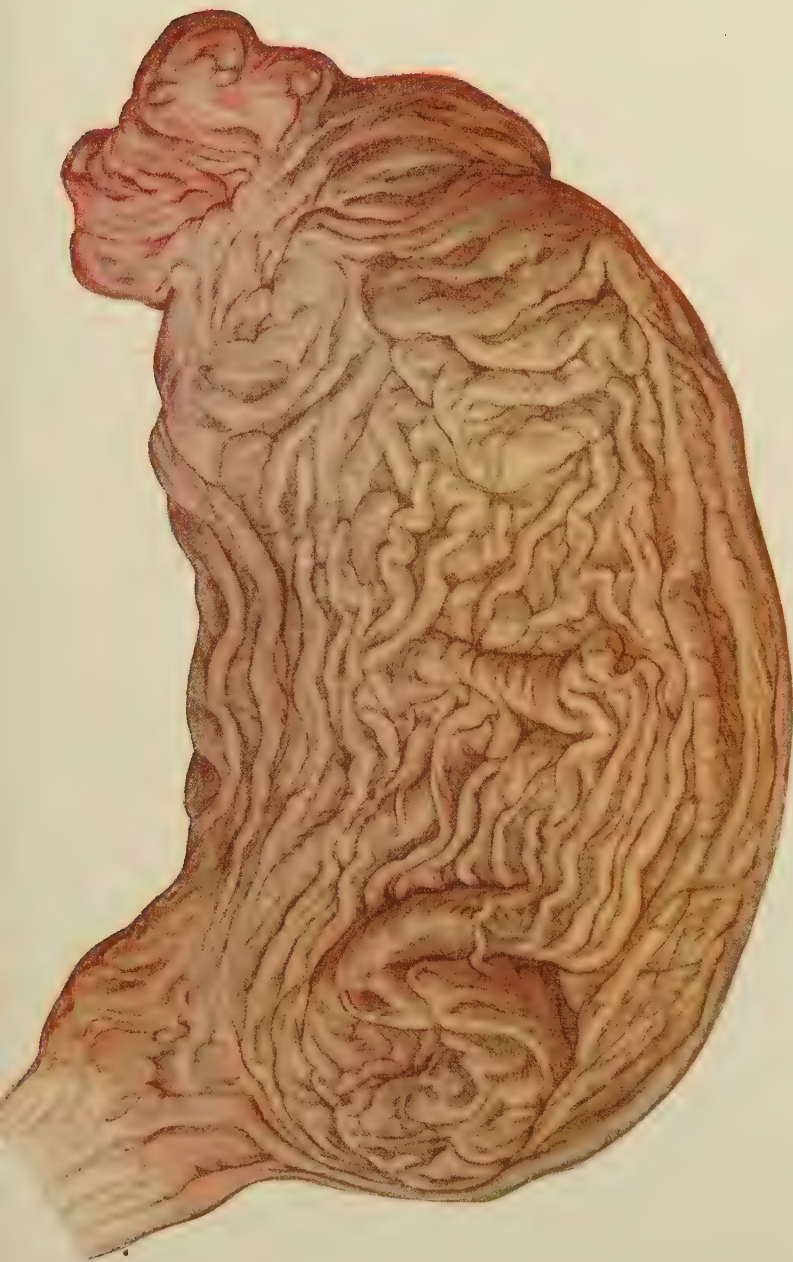
⁴ Jour. Amer. Med. Assoc., 1917, lxviii, 1024.

⁵ Ibid., June 19, 1915, lxiv, 2041.

⁶ Jour. Ind. Hyg., 1920, 2, 193-196; Jour. Amer. Med. Assoc., December 16, 1911.

⁷ Schamberg, Kolmer, Raiziss, and Gavron, Jour. Amer. Med. Assoc., January 19, 1918, lxx, 142.

⁸ Arch. f. Hyg., 1914, lxxxiii, 43.



STOMACH AFTER ACUTE POISONING WITH CORROSIVE SUBLIMATE (VON HOFMANN).

A hospital nurse poisoned herself with a concentrated solution of corrosive sublimate, and died from collapse in four hours after persistent vomiting. A grayish-white eschar was diffused over the mucous membrane of the lips, mouth, and pharynx. At the necropsy the same appearance was found in the esophagus and stomach. The stomach was firm and contracted, looking as if cooked. The entire mucous membrane and part of the submucosa were colored a uniform pale violet. The walls were thickened, and fell into coarse folds. The changes were those of "coagulation necrosis." The peculiar color is the result of the mouse-gray tint of the coagulated blood in the vessels, blending with the white escharotic tissue of the epithelium.

studied by him. Although the direct contact with the metal was in hand-working the amalgam for tooth-fillings there was no difference in the very small amount detected, whether the dentist worked with bare hands or gloved. The metal entered the body by the respiratory passages and did not affect the general health appreciably.

The symptoms shown in chronic mercurial poisoning are often quite complex. Ptyalism, or salivation, is usually present; the secretion of saliva is profuse, and is attended with swelling and tenderness in the salivary glands; the gums become red, spongy, and tender, with occasionally a blue line near the teeth; the tongue is swollen and painful; ulcers form in the mouth, and the breath is very fetid. The teeth are loosened, and the alveolar processes sometimes become the seat of acute periostitis. There is usually loss of appetite, with attacks of nausea and vomiting. In some cases colic and diarrhea are present. Soon supervene depressed energies, loss of weight, anemia, and a peculiar cachexia with eruptions of erythema or eczema. The nervous system is eventually involved, showing attacks of cerebral excitability and insomnia, or perhaps hebetude of mind. In the end a peculiar fine tremor spreads from the tongue and face to the upper and lower extremities. The tendency of these tremblings is to progress from the jerky and intermittent form, brought on by excitement or exertion, to the continuous, which lessens only during sleep. The muscles grow weaker, without loss of electrocontractility.

Disturbances of sensation are common; sometimes neuralgia is a symptom, at times appearing as numbness and tingling in anesthetic patches. Affections of sight and hearing are not infrequent.

The toxic effect induced by working with mercury in felting hats is shown in the report by Dr. Adler¹ of 5 cases, none of which was fatal. While all showed marked salivation, there was no diarrhea; the palsy began in the upper extremities and gradually involved the entire muscular system, except the muscles of mastication and deglutition. In one only was there a distinct blue line on the margin of the gums. Ankle-clonus was absent in all, and 4 had exaggerated knee-jerk. A typical case was a man of thirty-five, who had been employed for ten years as a hatter, during which time he had lost flesh from year to year. In that period he had frequent attacks of indigestion, his bowels were habitually constipated, though some of his associates suffered from diarrhea, and some had no control over the passage of urine. In August, 1889, he had the first attack of tremor, beginning in the hands and extending to the whole body. In his sleep he had horrid dreams and muscular twitchings. Sensation was unimpaired. The mobility of the tongue was seriously affected, his speech at times being barely intelligible. He had much difficulty in descending stairs. Having quit work for several months and taken salt baths, he improved, although he remained ataxic and tremulous, while vision was notably blurred. The breath was fetid, teeth loose, gums spongy, tongue tremulous, speech thick. There was no ankle-clonus, but exaggerated knee-jerk on both sides.

¹ Medical News, 1891, lix, 186.

The *postmortem appearances* correspond to the symptoms and indicate that mercury, like arsenic and lead, has the power to excite a progressive peripheral neuritis. The localized mercurial palsies differ from the lead palsies in that the electrocontractility is unimpaired, there is no atrophy, and the tendon reflexes persist. The characteristic nerve lesion is a destruction of the myelin, with preservation of the axis-cylinder. The trophic changes are pigmentary and peri-axile.

Treatment of Chronic Mercurialism.—Improvement usually follows removal of the patient from the surroundings where he was exposed to the poison. Although elimination of a single dose is usually complete in a few days by means of the salivary glands, the kidneys, the stomach, the intestines, and in less degree by the sweat and milk,¹ still, if the period of absorption has been prolonged, as it is in chronic mercurialism, some portion of the poison may be retained, combined with albuminous bodies in an inactive state² for many months. To stimulate the process of elimination and to secure the oxidation of the albuminous compound so as to set free the mercury, the bowels should be kept opened, the action of the skin promoted by warm baths, and the best hygienic and tonic regimen instituted. It is customary to administer potassium iodid in small doses in the belief that it changes the deposited poison into mercuric iodid, which is soluble in excess of the potassium salt, and is by this means conveyed into the excretory fluids. It is not easy to reconcile this custom with the results obtained by Souchow,³ who found that when a patient took potassium iodid with the mercurial the elimination of mercury commenced later, and the quantity eliminated was relatively less than when the mercurial was given alone. As it was also less daily if the iodid was given after the mercurial course, he concluded that the iodid did not facilitate the eliminating process, but rather retarded it, proving worse than useless in chronic mercurialism. For the paralysis, massage and electricity are indicated; for the salivation, mild mouth-washes of potassium chlorate or borax are called for.

Tests.—1. *Sublimation Test for Compounds in the Solid State.*—The suspected solid is first thoroughly dried, mixed with dry sodium carbonate, and heated gently in a reduction tube. A shining ring forms on the inside of the tube in the cooler part. A lens resolves this sublimate into minute shining spheres of metallic mercury. The corresponding sublimate of arsenic and antimony are not of this shape. Rubbed with a glass rod, these globules run together into larger rounded masses. A few scales of iodine left in the closed tube for a few hours will vaporize and convert the mercury into a film of yellow, and later of red, mercuric iodid. If this test is done in a small subliming cell, such as is described under Arsenic (p. 224), and collected on a slide for microscopic examination, it is of very great delicacy.

2. *Hydrogen Sulphid Test.*—A solution of a mercurial salt acidu-

¹ Byasson, Jour. de l'Anat. et de Phys., 1872, viii, 500.

² Voit, Physiol.-chem. Untersuch., 1857, p. 45.

³ Jour. de Pharm. et de Chim., 1887, 6 S., xv, 367; Bull. gen. de therap., 1887, cxii, 133; Vrach, 1886, vii, 840, 855.

lated with hydrochloric acid yields a black precipitate when treated with a stream of hydrogen sulphid. The formation of the mercuric sulphid through intermediate stages is shown if the tested solution is strong; the precipitate becomes successively yellowish white, dark yellow, orange, brown, and black. The precipitate is insoluble in caustic alkalis, alkaline sulphids, and nitric or hydrochloric acids. It can be identified by yielding the globular sublimate when dried and heated with sodium carbonate, as directed above. By drying the sulphid in an air-oven and weighing the quantity of mercury may be calculated.

3. *Reinsch's Test*.—The procedure is the same as that given under Arsenic (p. 223). A strip of bright pure copper-foil will receive a gray or silvery deposit in a few minutes from a boiling mercurial solution

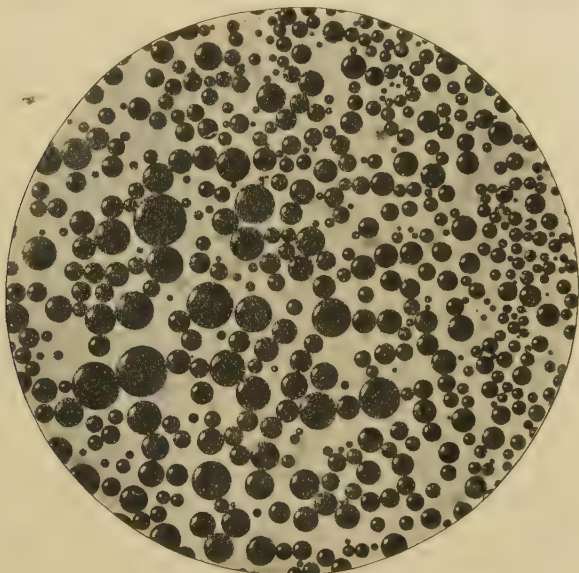


FIG. 30.—Sublimate of metallic mercury magnified.

acidified with hydrochloric acid. Having carefully washed the coated copper in water and dried it, the slip is heated in a small dry reduction tube, and the resulting sublimate examined for globules and tested with free iodine. Certain of the organic mercurials may not readily respond to this test.

Fallacies.—This test yields a metallic deposit on copper from arsenic, antimony, bismuth, silver, and some rarer metals. Coatings of arsenic, antimony, and mercury are the only ones that give a sublimate when heated in a reduction tube.

Mercury is peculiar in its opaque globular form and the bright high lights under reflected light.

Delicacy.—Using capillary reduction tubes of peculiar construction, Wormley¹ has obtained characteristic globules from $\frac{1}{500000}$ grain of

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 350.

corrosive sublimate; under ordinary manipulation $\frac{1}{100000}$ grain is nearer to the limit of delicacy.

4. *Galvanic Gold Test*.—A band of gold-foil is wrapped about a strip of thin zinc, leaving some zinc exposed, thus making a galvanic couple. Having acidulated the suspected liquid with hydrochloric acid and warmed it, the two metals are hung in it for several hours. A silvery deposit on the gold indicates mercury. After washing the gold successively in water, alcohol, and ether, it may be heated in a reduction tube, and the sublimate of mercurial globules produced may be identified, as stated under Sublimation Test.

5. *Potassium Iodid Test*.—On adding potassium iodid to a solution of corrosive sublimate or other mercuric salt, a precipitate falls, at first yellow, but rapidly changing to red mercuric iodid. This will dissolve in excess of the potassium iodid.

Distribution in the Tissues.—Riederer¹ gave to a dog in thirty-one days 2.789 grams of calomel (2.368 gm. Hg). By analysis he recovered 2.2 grams of mercuric sulphid (1.9 gm. Hg), of which there were in the feces 95 per cent., or 2.1175 grams; in the urine, 0.055; in the brain, heart, lungs, spleen, pancreas, kidneys, scrotum, and penis, 0.009; in the liver, 0.014; in the muscles, 0.0114. If the poison finds access to the body by external application or by irrigation of other cavities than the alimentary tract, it should be looked for in the liver, the urine, and the kidneys. In the case of acute poisoning from corrosive sublimate reported by Church,² cited above, a chemical examination was made of the nasal mucus, the gastric and duodenal contents, the pleural serum, the feces six hours before death, a portion of the liver and one kidney, and not a trace of mercury could be detected. It would appear that in the twenty-two hours which elapsed between the administration of the poison and death total elimination had occurred, though it is possible that the chlorid had been reduced and the metallic globules remained undissolved by the chemical procedures. Other cases have been reported which established the fact that in a few days the whole amount of one poisonous dose given by the mouth may escape from the body. Kahn, Andrews, and Anderson³ reported a case of rapid death from mercuric chlorid, 25 to 50 grams, in which the post-mortem revealed mercury in every tissue except the skin, hair, and nails. The largest tissue percentages were obtained respectively from the liver 19.3, kidneys 13.7, intestines 8.4, spleen 8.4, adrenals 4.2, brain 3.7. The colonic washings collected as much as 10 per cent. of the dose.

There is liability to error if the analyst loses sight of the well-known fact to which Taylor⁴ has drawn attention—*i. e.*, that traces of mercury are very commonly found in the stomach, bowels, liver, kidneys, and other organs of the cadaver with no history of recent dosage from the

¹ Buchner, Neues Rep. f. Phar., 1868, 17, 257.

² Edin. Med. Jour., 1887, xxxii, 795.

³ Med. Record, New York, 1915, 88, 357.

⁴ A. S. Taylor, Principles and Practice of Medical Jurisprudence, 12th Am. ed., 1897, p. 148.

poison. These are probably accumulations from small non-poisonous doses of blue-mass, compound cathartic pills, or calomel, or perhaps vestiges of a previous mercurial treatment of syphilis.

Detection.—Mercury will probably be found in all the excreta, as albuminate. A ready, casual examination can be made of the vomited matters or urine by decanting the liquid portion, evaporating it to dryness, treating with pure hydrochloric acid, and applying Reinsch's test, the galvanic gold test, or the electrolytic test.

Separation from the tissues or other organic matter is accomplished by the systematic method referred to under Arsenic. To disintegrate the organic matter thoroughly, it must be finely minced and heated on a water-bath for some time with equal parts of water and hydrochloric acid, while potassium chlorate is added in small amounts until a clear solution is made.¹ After filtration the solution is heated gently to expel the chlorin, and a stream of hydrogen sulphid is passed until the metal is all precipitated as sulphid. A portion of this sulphid may be tested by reduction and sublimation, or it may be dissolved by gentle heat in nitrohydrochloric acid, the solution evaporated to dryness on a water-bath, redissolved in warm water, and the above tests be applied or the mercury separated by electrolysis.

Electrolysis may be performed conveniently by the method of Mann.² The suspected solution is put in a glass cell having a bottom of parchment paper, and immersed to a common level in an outer vessel of water acidulated with sulphuric acid. The cathode of a battery of four Grove cells, made of a slip of gold-foil, is fixed into the inner vessel near to, and parallel with the bottom. In the outer liquid is set the anode, a strip of platinum opposite to the cathode. After the current has passed six hours, the gold coated with mercury is washed successively with water, alcohol, and ether, and weighed. By heating the gold-foil in a hard glass open tube of known weight the mercury sublimates and is deposited on the tube.

Quantitative determination may be made by finding the loss of weight of the gold-foil carrying a film of mercury when heated as above described. This gives the weight of mercury in the portion of fluid tested; it can be controlled by calculating the increase of weight in the tube. Instead of using electrolysis, the amount of corrosive chlorid present in any fluid in which mercury is sought may be determined simply by boiling the materials in water, straining, filtering, and agitation of the filtrate with ether, separation, and evaporation of the ethereal extract. The dried residue dissolved in water may be precipitated with volumetric solution of silver nitrate, the chlorin estimated, and from this the weight of mercuric chlorid calculated. Waldbott³ precipitates mercury from dilute acid solution upon clean copper foil, as in Reinsch's test. The foil is dried and weighed. Mercury is driven off by holding the foil *above* a flame until the gray film has just disappeared.

¹ Consult also p. 46 et seq. in section on General Principles of Toxicology.

² J. D. Mann, Forensic Medicine and Toxicology, Philadelphia, 1893, p. 453.

³ Science, 1919, 1, 441.

The difference in the two weighings represents the mercury present. From a nitric acid solution as much as 99.83 per cent. of mercury has thus been recovered.

Volumetric Determination.—Low¹ found titration by potassium thiocyanate satisfactory if chlorine and bromine were absent. Having precipitated mercuric sulphid as in Test 2 and having washed it and rinsed it from the filter into a 250 mls. (c.c.) flask with the least possible quantity of hot water, add 5 or 6 mls. (c.c.) of concentrated sulphuric acid and 0.5 gram or less of potassium permanganate crystals. Boil and shake it over a flame until the acid strongly fumes. Remove from the flame and add oxalic acid crystals until the manganese oxid is dissolved. Again heat and agitate until strong fumes arise to destroy the excess of oxalic acid. Cool, dilute with 100 mls. (c.c.) of cold water to make a clear solution. At room temperature add indicator (5 mls. (c.c.) concentrated solution of ferric-ammonium sulphate acidified with nitric acid) and titrate with 0.1-N thiocyanate solution to a faint brown tint. One mil. (c.c.) used = 0.01 gram mercury.

Urine examination may be made by electrolysis, by Reinsch's test, alone or combined with the gold-leaf test as in the method of Vogel and Lee² which oxidizes the organic matter by heating with hydrochloric acid and potassium chlorate; precipitates the mercury from the acid solution upon copper wire and then sublimes the mercury to be collected upon gold foil in the upper part of the narrow test-tube. This test is sensitive in the proportion of 1 : 100,000. Elliott³ has modified this test for urine work so that it detects $\frac{1}{1000000}$ grain of mercury dissolved in 500 c.c. of distilled water, dispensing with the oxidizing of the organic matter and subliming the mercury upon gold leaf in a special tube. Mayer's method is as follows: Having evaporated the urine to dryness, the residue, mixed with quicklime and slaked lime, is heated in a combustion tube, condensing the mercury on the cooler part. Another method is described by Lombardo: One drop of egg albumin is added to 5 mls. (c.c.) of filtered urine and agitated. To reduce the mercury tin chlorid is added, 3 mls. (c.c.) of a 12 per cent. solution just filtered and hyperacidified with 25 per cent. of hydrochloric acid. The urine becomes turbid and finally opalescent. Rotated in a centrifuge the precipitate is collected and examined under 600 diameters of magnification. Metallic mercury appears in very minute black globules.

COPPER

(Chemical Symbol, Cu; Synonym, *Cuprum*.)

This element is a heavy reddish metal, which dissolves in nitric acid, in hot sulphuric acid, and, when exposed to the air, is soluble also in hydrochloric acid and in ammonia. Even distilled water will, in time, take up some. One hundred c.c. may dissolve 0.3 mg. of copper or

¹ Chem. Analyst, 1920, 29, 13-4.

² Jour. Amer. Med. Assoc., 1914, lxii, 752.

³ Jour. Amer. Med. Assoc., 1917, lxxviii, 1693. See also Autenrieth and Montigny, Münch. med. Wehnschr., 1920, 67, 929.

0.2 grain in a gallon.¹ Natural waters containing salts, especially the chlorids, exert still more solvent powers. The syrups and fats dissolve it, and the fatty acids readily combine with it. Vinegar, acid wines, and subacid fruits kept for a few hours in copper vessels are found to contain the metal.

Distribution in Nature.—Not only is copper to be found in native masses and in its ores—the carbonates, oxids, and sulphids—but in minute proportions it is a constituent of many common minerals and soils. Natural water takes up a trace, and vegetation thus derives it from soil and from water. Careful analysis has detected it in edible roots, such as the turnip, in fruits, berries, salads, wheat, barley, and other cereals, coffee, chocolate, and quiniñ. From plants as food it is found to be derived by animals—domestic and wild. Oysters, clams, crabs, and other sea-food show a trace. Constantly present in our chief foods, it is not surprising that it is found in the body of man. Ryan² found it a constant constituent of liver tissue as a product of food derivation. Stored there as a stable nucleinate it is excreted very slowly. That it does not fulfil a physiologic need is apparently shown by its absence in the case of 54 normal human livers from subjects of a different environment, and dietary from Ryan's, reported by Palet,³ of Argentina. Bodansky⁴ finds that copper, as well as zinc, is a normal constituent of the human brain. In their analyses of the ashes of all ordinary vegetables, of egg yolk and horse meat, of wheat from all sources, as Russia, Taganrog, and near Paris, Fleurent and Levi⁵ detected copper regularly. They thought it probable that copper played a catalytic rôle in protoplasm like that of manganese. Leaving out of the count foods possibly contaminated artificially, Blyth⁶ estimated that each of us takes daily about 1 mg. (0.015 gr.) of copper. While the metal itself is not to be considered as a poison, its salts, in large doses, act as irritants, and in small amounts continuously administered retard normal metabolism.

Forms.—The irritant salts are copper sulphate (blue vitriol), copper subacetate (verdigris), and copper aceto-arsenite (Paris green). As the poisonous properties of the last named are dependent chiefly upon the arsenic, it is considered among the compounds of that metal.

Copper sulphate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$), commonly known under the trivial name of "blue-stone," occurs in large, blue, slightly efflorescent crystals, freely soluble in water, and having a strong metallic taste. It is used in medicine as an external application, for its astringent or mild stimulating qualities. Internally, in doses of $\frac{1}{4}$ grain to 2 grains it is given as a tonic and astringent; in doses of 5 to 10 grains, it acts as a prompt emetic. It is employed in phosphorus-poisoning as an antidote and also as an emetic. In very large doses it is poisonous, and has been used both for suicidal and for homicidal purposes.

¹ Carnelley, Jour. Chem. Soc., 1876, ii, 4.

² Univ. Pa. Med. Bull., June, 1907, xx, 53.

³ Sem. méd., Buenos Aires, 1919, xxvi, 151; Chem. Abst., 1920, xiv, 3710.

⁴ Jour. Biol. Chem., 1921, 48, 361.

⁵ Bull. Soc. Chim., 1920, 27, 440.

⁶ A. W. Blyth, Poisons, Effects and Detection, 4th ed., 1906, p. 640.

Copper subacetate ($\text{Cu}_2\text{C}_2\text{H}_3\text{O}_2, \text{CuO}$) in an impure form is known as "verdigris." The same name is popularly given to other green salts of copper, as the oleate and carbonate. Verdigris in medicine is used only externally. In the arts it is frequently employed.

Symptoms of Acute Poisoning.—The very disagreeable taste of copper salts prevents the frequent criminal use. Out of 42 cases,¹ which were authentic, 1 was from application to the scalp, 1 from insertion of copper sulphate into the vagina, and 40 were internal. Of these 40, 4 were accidental, 19 suicidal, 15 were homicidal, and in 2 intent was not stated. The onset of the symptoms may be said to begin with this coppery astringent taste and the feeling of tightness in the throat. In a few minutes nausea and violent vomiting of greenish matters begin. Soon appear thirst, pain in the stomach, and colic, with violent purging of stools having the same green hue of the vomit. Ammonia-water added to the green excreta will turn them blue, and thus distinguish this copper-green from bile. The urine is scanty and may become albuminous, inky from changed hemoglobin, and loaded with tube-casts. The later stages are characterized by nervous phenomena, such as pains, spasms which may be tetanic, paralysis, delirium, and collapse. In the course of a few days jaundice appears as a result of involvement of the liver.

Fatal Dose.—Owing to the energetic emetic properties of large doses of copper sulphate, evacuation of the stomach is so prompt that we have no means of determining how much would prove fatal. On the one hand, a child four and a half years old has recovered after a dose of over $\frac{1}{2}$ ounce of copper sulphate; on the other hand, an adult has succumbed to a dose of $\frac{1}{2}$ ounce of verdigris.

Fatal Period.—As a rule, life is prolonged for several days, the patient sometimes almost recovering from the symptoms of gastro-enteric irritation and finally dying from the effects of the absorbed poison. Copper sulphate has caused death in four hours.

Treatment.—Evacuation of the stomach must first be obtained by stimulating the natural effort at vomiting. The antidote is the albumin of egg or the casein of milk. Eggs beaten in warm water should be given freely. If vomiting does not occur or is not active, the stomach-pump should be resorted to and the stomach washed out with milk or eggs and water. A milk diet with castor oil will favor removal from the intestine.

Postmortem Appearances.—Congestion, swelling, softening, and excoriations of the mucous membrane of the stomach and bowels are usually found. The colon sometimes shows large ulcerations. A bluish discoloration of the lining membrane indicates that all the copper has not been evacuated. The liver may be soft and fatty, the kidneys swollen, and the tubules closed with bloody casts. In a case reported by Starr² the blood of the entire body was found coagulated in the vessels and changed to a chocolate color.

¹ Witthaus, *Manual of Toxicology*, New York, 1911, p. 710.

² *Med. Record*, 1882, xxi, 564.

Chronic Poisoning.—It was thought, until comparatively recent times, that the slow introduction of minute doses of copper was injurious to the tissues by causing such pathologic changes as are known to be due to certain other poisons, such as phosphorus, arsenic, antimony, lead, and mercury. It has been proved by Bernatzic¹ that as a slow poison copper belongs to a different category—that of silver and zinc. To produce toxic phenomena it must be given freely and intentionally. After a long course there are functional disturbances of the muscular and nervous systems, anemia, and cachexia. As soon as the administration ceases the functions are restored and the subject slowly but spontaneously recovers from the cachexia. Moulin² states that it has not been demonstrated that any doses, however large, which have been taken with food have ever caused death, while medium doses in the beginning act as simple emetics, tolerance is rapidly established, and administration can be continued for six months without danger of chronic disease. Lehmann³ experimented upon himself and his pupils with the sulphate and acetate, and found that a man could take 75 to 127 mg. (1-2 gr.) of copper in peas and beans daily, divided in two meals, without obvious injury.

Copper salts were extensively used to impart a lively green color to pickled cucumbers and canned peas and beans. A permanent green compound is formed between copper and an acid derivative of the chlorophyll in the vegetable. It being thought desirable to continue this esthetic appeal and appearance of freshness, elaborate researches were carried out in various countries under the highest sanitary authorities to settle the limit of copper admissible as not injurious to health. Moulin⁴ thought that the amount necessary to give the attractive color is absolutely harmless. This opinion was sustained by the Council of Hygiene, composed of Pasteur, Poggiale, and Brouardel, who reported⁵ that "copper in the amounts found in canned goods is not capable of injury to health." On the other hand, the International Congress of Food Analysts⁶ declared against it and the governments of Germany and Austria forbid its use. The investigations of the United States Department of Agriculture led to the conviction that copper sulphate used for the greening of vegetables is injurious.⁷ It regards as adulterated all foods so treated, and forbids their importation or shipment by interstate commerce. This action was based on the report of the Referee Board of Consulting Scientific Experts,^{8,9} which found that even when the experimental diet was carefully freed of food artificially coppered there was a measurable output of copper in the feces of all seven of the subjects, without doubt contributed by

¹ Encyc. d. ges. Heilkunde, xi, p. 429.

² Jour. de Méd. de Paris, 1887, xiii, 652.

³ Münch. med. Wchenschr., 1891, xxxviii, 603, 631.

⁴ Op. cit.

⁵ Annales d' Hyg., 1880, 3 S., iii, 193.

⁶ Ztsch. f. Nahrungsmittel chem., 1891, 557.

⁷ Food Inspection Decision 149, December 26, 1912, Washington.

⁸ Rept. No. 97, U. S. Dept. of Agric., 1913.

⁹ Jour. Amer. Chem. Soc., January, 1914, p. 132.

the ordinary foods, such as cereals and vegetable products. When the diet was arranged to include artificially coppered vegetables, the amount in the feces and the urine was so much less than that known to be ingested as to prove the distinct retention in the tissues. The small proportion found in the urine indicated slow elimination. Taking 10 to 12 mg. of copper as the upper limit of the "small quantity" which ordinarily would be in the "greened" vegetables daily consumed, they concluded that even such small quantities of copper continuously taken may have an effect prejudicial to health and digestion as indicated by the ordinary clinical and medical summaries.¹

Workers in copper or its compounds, such as malachite, are liable to a disease called "copper colic," which differs from lead colic in that diarrhea is present instead of constipation; there is greater prostration, its duration is shorter, and the prognosis good. It is maintained by able investigators that such symptoms are not due to copper, but to the lead and arsenic which are impurities in most ores and in the commercial metal, or to the lead in the solder used by the operators. This is borne out by the fact stated by Chevallier, that after more than one attack "drop-wrist" or lead-palsy is apt to supervene. According to Milton,² no symptom-complex of poisoning is found in certain copper workers, who show copper as a purplish or bluish line on the gums, whose hair turns green, and whose urine stains the ground green. In regard to a well-defined syndrome, Tschirch³ sums up the evidence as follows: "So it appears the contention that there is no chronic poisoning in men or animals is at present uncontradicted."

Tests.—1. *Hydrogen Sulphid Test.*—A stream of hydrogen sulphid passed through an acid solution of a copper salt yields a brownish precipitate of copper sulphid, freely soluble in warm nitric acid, slightly so in excess of ammonium sulphid, but insoluble in the caustic alkalis.

2. *Ammonia Test.*—A solution of a copper salt is either green or blue. By adding ammonium hydroxid in excess to a slightly colored solution, cupric hydroxid is formed, and dissolved to make a much deeper sapphire-blue solution.

Fallacies.—The salts of nickel give the same deep blue solution.

*Delicacy.*⁴—The change in color is recognizable in 1 grain of a solution containing $\frac{1}{5000}$ grain of copper oxid.

3. *Potassium Ferrocyanid Test.*—This reagent precipitates from a strong copper solution the reddish-brown copper ferrocyanid. When the solution is very dilute no precipitate falls, but the solution turns reddish-brown. The brown precipitate is insoluble in acetic and hydrochloric acids, but with ammonium hydroxid forms a greenish-blue liquid.

¹ H. W. Wiley, Proc. Amer. Phil. Soc., May, 1908, p. 322.

² Buck's Hygiene, New York, 1879, ii, 50; See also Houllés, Jour. d. Hyg., 1879, iv, 160, 170.

³ Das Kupfer, Stuttgart, 1893. See Mallory, Parker, and Nye (Jour. Med. Res., 1921, 42, 461) for experimental work on rabbits resulting in the production of a pigmentary hepatic cirrhosis resembling that found in human hemochromatosis.

⁴ Wormley, Micro-Chemistry of Poisons, 1885, p. 389.

Fallacies.—Solutions of uranium salts yield a similar brown precipitate, but when this is treated with excess of ammonium hydroxid, the liquid is yellow, not blue.

Interferences.—A trace of iron will give a blue color with this reagent and thus mask the result.

*Delicacy.*¹—A distinct red reaction can be obtained from $\frac{1}{25000}$ grain of copper oxid.

4. *Iron Test.*—This test separates copper in the metallic state. It is performed by immersing a steel needle or other piece of bright steel or iron in the suspected liquid slightly acidulated. If copper is in solution, it will be deposited as a reddish layer on the iron. To prove that this film is copper, it is dipped in ammonium hydroxid and exposed to the air, when the film of copper turns blue.

5. *Galvanic Zinc Test.*—Very delicate results can be obtained by immersing in a copper solution a galvanic couple made by wrapping platinum wire around a piece of zinc-foil. The platinum is soon discolored by a deposit the nature of which can be established by exposing it to the vapors arising from potassium bromid when treated with sulphuric acid. The deposit changes in color, and if rubbed on white porcelain leaves a violet mark.

Delicacy.—According to Blyth,² $\frac{1}{100}$ milligram of copper in solution can be recognized by this test.

6. *Electrolytic Test.*—Having obtained the copper in solution and concentrated it, make it acid with hydrochloric acid, and put it in a weighed dish of platinum which is connected with the zinc pole or cathode of a battery. A strip of platinum-foil as anode is immersed in the tested solution for twenty-four hours. In that time all the copper will be deposited on the platinum dish. To make a quantitative estimate the dish must be washed, dried, and weighed again. The gain represents the total amount of copper in the volume of tested solution.

Separation from Animal Matters.—The organic matter in the contents of the stomach or in the liver, brain, or other tissues must be destroyed by burning to an ash and extracting with nitric acid, or by boiling with hydrochloric acid and potassium chlorate, according to the systematic procedure given under arsenic.³ By evaporation the excess of acid can be removed, and the residue, dissolved in acidulated water, may be tested by the methods given above.

BISMUTH

(Chemical Symbol, Bi.)

The study of the toxic action of bismuth is practically that of the salt most commonly used in medicine, the *subnitrate*. This is a heavy, white, tasteless, insoluble powder, sometimes used as a cosmetic under the name of "pearl white." It is much used as a local sedative for gastric and intestinal irritation, and is given almost *ad libitum*. At one

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 392.

² A. W. Blyth, *Poisons, Effects and Detection*.

³ Consult also p. 46, in Section on General Principles of Toxicology.

time most samples were imperfectly freed from the arsenic, which is found associated with bismuth in its ores.¹ Antimony, lead, and a trace of tellurium have been found in it.¹ The *subcarbonate*, a yellowish-white insoluble powder, is often given for the same indications as the subnitrate. Large doses of both have been given suspended in milk or water as a meal contrast in Roentgen work.

Symptoms.—While the salt itself has no taste, yet in cases of poisoning a peculiar metallic taste is complained of, accompanied by salivation, foul breath, and sore mouth. There are vomiting, abdominal pain, and purging of stools, dark from bismuth sulphid. Sometimes a black discoloration appears upon the gums, and may spread over the whole mouth.

The strong garlicky odor of the breath sometimes observed has been attributed to tellurium, which produces this effect, although the amount is very minute. As the gastro-enteric symptoms are similar to those of arsenic, the toxic action of bismuth was at one time ascribed to that impurity. Dreesman² cites cases showing that large doses internally, as well as free topical applications of bismuth salts, have caused black urinary sediment, albuminuria, and tube-casts, besides the usual stomatitis, loosened teeth, blue gingival line, diarrhea, and ulceration of the intestines. A man thirty years old was treated for a severe burn with local applications twice daily of a 10 per cent. ointment of bismuth subnitrate. Within the first three weeks the urine showed black deposits. During the second three weeks there was stomatitis, with pain on swallowing, loosened teeth, and a bluish-black discoloration on the gums and tongue. As the preparation was free from lead, arsenic, or other contaminant, the symptoms were plainly due to absorbed bismuth. In 2 infants of one and two years³ the poisonous symptoms from internal administration of the subnitrate were cyanosis, diarrhea, dyspnea, and death from arrest of respiration without any of the usual bismuth mouth symptoms. Zollinger attributed these cyanotic symptoms to the nitrite ion formed. Experimental research⁴ has shown that the nitrate ion in this salt is reduced to nitrite by infant feces, but not by adult feces. Nitrites produce methemoglobin and other color changes in the blood, with cyanosis and collapse. Nitrites were present in the blood and the pericardial fluid after experimental poisoning with the subnitrate.⁵

Two cases have been described by Dalche,⁶ which show peculiar effects on the mouth, due to the fact that bismuth is eliminated largely by the saliva. These cases are remarkable because equally large amounts administered by the mouth have been without injurious consequences. This is explicable on the theory that the bismuth salts are more readily absorbed from granulating surfaces than from sound mucous mem-

¹ Braithwaite, Amer. Druggist, 1884, 13, 88.

² Berlin. klin. Wochenschr., 1901, xxxviii, 924.

³ Zollinger, Jour. Amer. Med. Assoc., 1912, lviii, 901.

⁴ Böhme, Arch. f. exp. Path. u. Pharmacol., 1907, lvii, 441.

⁵ Jonescu, Chem. Abstr., 1921, xv, 120.

⁶ Annales d'Hyg. Pub., 1886, 3 S., xvi, 358.

branes because the exuded fluid forms bismuth albuminate, a soluble compound. In one case an extensive burn was treated with local applications of bismuth subnitrate, proved by analysis to be pure. In two weeks there was a severe inflammation of the mouth and throat, with adherent black exudations; vomiting and diarrhea supervened with albuminuria. Bismuth was detected in the urine and the feces. A few days after the application was discontinued the acute symptoms subsided. The second case, after excision of the knee, had the wound dressed with bismuth subnitrate. In a fortnight there were salivation and stomatitis, with bismuth in the urine. An experimental research on the lower animals, using a pure salt of bismuth hypodermically, caused death after symptoms like those just described.

During the World War a bismuth paste was applied by the British service to hundreds of infected wounds. It was called "bipp" from the initials of its components—bismuth, 1 part; iodoform, 2 parts; liquid paraffin, 1 part. Morison¹ reported that out of hundreds so treated in war hospitals only 3 had "blue gum" with stomatitis attributable to absorbed bismuth, and of these there were no fatalities.

Formerly the use of massive doses of bismuth subnitrate or subcarbonate, to serve as contrast meals in Roentgen work, has sometimes occasioned toxic symptoms. The records of all modes of internal administration² up to 1916 show 21 toxic cases, with 14 fatalities. Most of the recent reports of bismuth-poisoning state the cause to be local applications of bismuth-vaselin paste (bismuth 33 per cent.), especially to chronic suppurating sinuses and empyema as advocated by Beck.^{3, 4, 5, 6} Brilliant cures have resulted from this method, which has besides the merit of a simple and painless technic. David and Kauffman⁷ reported 2 cases of bismuth poisoning, with 1 fatality, due to injecting the Beck paste into discharging sinuses. The characteristic salivation, stomatitis, and green-blue discoloration of the gums, tongue, and buccal lining were present together with gastro-intestinal irritation. Reviewing the literature of such cases, Mayer and Baehr⁸ in 1912 collected 64 that were toxic, with 24 deaths. Since then there have been reported at least 6 cases, with 2 deaths. Beck⁹ in 1916 drew attention to a series of 1800 patients treated with bismuth paste in the North Chicago Hospital without a single fatality. He maintained that the mishaps are due to the surgeon's carelessness and faulty technic or the patient's idiosyncrasy. In a hospital, with frequent observations, an early detection of the blue gingival line and stomatitis is likely. This would call for prompt and thorough removal of the paste from the sinus, when all the symptoms usually disappear. That this

¹ Brit. Jour. Surg., 1917, iv, 659.

² Higgins, Jour. Amer. Med. Assoc., 1916, lxvi, 648.

³ Ill. Med. Jour., July, 1908, xiii, 402.

⁴ Jour. Amer. Med. Assoc., 1909, lii, 14.

⁵ Ann. Surg., February, 1914, lix, 145.

⁶ Jour. Amer. Med. Assoc., 1916, lxvii, 21.

⁷ Ibid., 1909, lii, 1035.

⁸ Surg., Gyn., and Obst., 1912, 15, 309.

⁹ Jour. Amer. Med. Assoc., 1916, lxvii, 21.

method has remedial value is universally conceded, but its effects are not limited to the diseased locality and it cannot be considered innocent of harm. When 30 per cent. of over 1000 patients so treated showed pigmentation of the gums, there is evidence of frequent systemic absorption which might affect injuriously important organs that are in an impaired or sensitive condition. The surgeon, knowing this risk, will decide for the less of the possible evils, take all proper precautions, and hold fast that which is good.¹

Elimination is mainly by the gastro-intestinal tract and the kidneys. The metal has been detected in the bile, milk, and saliva.

Postmortem Appearances.—The most striking lesions are the brownish-purple patches on the tongue, the lining of the mouth and throat. These spots may be covered with a sticky white membrane. The teeth are loose and gums spongy, as in poisoning by lead and mercury. Mayer and Baehr² held a necropsy upon a death six weeks after the injection of 3 ounces of bismuth-vaselin paste. The mucosa of the small intestine showed areas of inflammation and necrosis. The steel-gray color studied with a lens was seen to be stippled with fine black points. The large intestine was coated with a greenish-black membrane, while underneath there was ulceration and necrosis. The liver cells showed cloudy swelling and disintegration. The tubular epithelium of the kidneys was degenerated so that the lumina were choked with cellular débris. The renal capillaries were intensely congested.

In a case of this sort,³ dying with the syndrome of uremic convulsions and coma, the autopsy revealed, in addition to the usual oral and gastro-intestinal lesions, general hyperemia of the brain cortex.

Fatal Dose.—The earlier reports as to the fatal dose must be taken with much allowance, owing to the fact that until recent times the bismuth salts almost always contained enough arsenic to cause trouble if the dose was a liberal one. Death has followed a dose of 2 drams. The period of fatality was the ninth day. A dose three times as large has been recovered from.

Tests.—Hydrogen sulphid yields a black precipitate of bismuth sulphid. If this is dissolved in the smallest possible quantity of hot nitrohydrochloric acid and the resulting solution poured into an excess of water, a copious white precipitate of bismuth oxychlorid is thrown down.

Extraction from the tissues is done by boiling the finely divided matter for two hours in dilute nitric acid, the dissolved material separated by filtration, and the filtrate evaporated to dryness. The undissolved organic matter is destroyed with strong nitric acid and then boiled with dilute nitric acid, filtered, and dried.

¹ The following references supplement those already given: Kobert, *Lehrbuch der Intoxic.*, 1906, ii, 385. Baccus, *Jour. Amer. Med. Assoc.*, 1909, lii, 1273. Pancoast, *Univ. Penna. Med. Bull.*, 1906-07, xix, 132. Camerer, *U. S. Naval Med. Bull.*, 1911, v, 59. Ely, *Med. Record*, New York, 1912, lxxi, 119.

² *Surg., Gyn., and Obst.*, 1912, xv, 309.

³ *Ellenberger, Zentralblatt f. Chir.*, Leipsic, 1908, xxxv, 1309.

A solution of both residues is made in 50 per cent. nitric acid and the above tests are applied.¹

ARSENIC

(Chemical Symbol, As; Synonyms, *Arsenum*; *Arsenicum*.)

Poisoning by some arsenical compound is often resorted to by the secret homicide, and comes under notice of the courts more frequently than any other form. In 1000 cases reported² from the years 1752–1911, 426 were homicidal, 230 were suicidal, 200 were accidental, 33 to produce abortion, 4 through mistakes of quacks, and 107 motive unknown. Taking suicides and homicides together, it has caused more deaths than any other poison except opium and its derivatives. During the seventeenth century a strong solution of white arsenic, known as *aqua topkana*, was widely employed by the poisoners of Italy and France, who were convicted only by self-confession. In spite of the fact that modern chemistry finds it the easiest of all poisons to detect, it is still used not only by suicides, but by criminals, many of whom escape punishment for years. Frau van der Linden pursued her nefarious career for fourteen years.³ In Leyden, between the years 1869 and 1883, she is estimated to have poisoned for their insurance money 70 persons, of whom 24 died, including her father, mother, and son. Within a period of eighteen months Mrs. Robinson, of Somerville, Mass., assisted by a quack doctor who knew something about arsenic, poisoned in succession 5 persons of her own family without exciting suspicion until her sixth victim died. Of 8 deaths of trusting friends laid to her charge, arsenic was found in the cadavers of 6. Mrs. Sherman, of New Haven, Conn., succeeded in escaping suspicion while she killed 3 husbands and 8 other persons of her immediate household with arsenic. The peculiar death of her fourth husband led to her conviction.

An instructive series of cases of wholesale poisoning in Havre was investigated by Brouardel, Pouchet, and others.⁴ A commission of four experts appointed to decide if certain premises used as a drug-store were unsanitary, reported that the symptoms of chronic ill health ascribed to the state of the house were in reality due to arsenical poisoning. It was then discovered that a clerk, in the course of two years, without exciting suspicion, had poisoned 15 persons, 3 of them fatally. They that survived, after running the gauntlet of severe disturbance of health, with lesions of the digestive, cutaneous, and respiratory apparatus, were left more or less completely paralyzed.

Arsenic, or ratsbane, is a favorite poison because it is cheap, can be bought as a vermin-killer at any drug-store in the United States, and

¹ See Aubry (Jour. pharm. chim., 1922, 25, 15) for the detection of bismuth in the urine.

² Witthaus, Toxicology, 1911, p. 413.

³ Amer. Jour. Med. Sci., October, 1886, cxviii, 614; Zaaier, Vrtljsch. f. ger. Med., 1886, n. f., xlv, 249.

⁴ Annales d'Hygiene, 1889, 3 S., xxii, 137, 356, 460; Brouardel, Les Empoisonnements, 1902, p. 58.

owing to its very feeble taste, can be mixed with the food without the victim recognizing the foreign ingredient. The acute symptoms simulate indigestion or *cholera morbus*, and thus the physician is misled. The practice of undertakers in some states of America is to inject sodium arsenate or other arsenical preparations into the viscera of a corpse to prevent decay. This usually makes an insuperable difficulty in the way of conviction, and knowledge of this fact must often embolden the criminal. Such practice is, however, prohibited by law in many states of the Union.

The reports of the Registrar-General of England show 51 deaths from arsenic in England and Wales in five years. Counting the number of poison cases thought worthy of record in the medical journals of the world in 1880–1889, arsenic figured in 8.3 per cent., poisonous foods in 8.7 per cent., and lead in 10.5 per cent.¹ It is stated² that in the decade 1879–1889 there were 12 indictments for murder by poison in 31 counties of New York State, in 6 of which the poison alleged to have been given was arsenic, in 1 it was strychnin, and neither morphin nor phosphorus was mentioned. Analyzing 820 cases, Witthaus found 45.2 per cent. homicides, 27.3 suicides, and 27.5 per cent. accidental. In the absence of rigid restrictions upon the sale of arsenical compounds, such as are imposed by other governments, the United States has a bad eminence in this respect. The Massachusetts reports give a list of 114 deaths in ten years in that state alone. Only 9 of these were proved to have been homicidal. There were 35 suicides from arsenic in New York City in one year (1891).

Arsenum or Arsenicum.—Free or elementary arsenic is a steel-black mineral with a metallic appearance, when oxygen is excluded, subliming at 400° C. (752° F.), and when burned in air, at 180° C. (356° F.), emitting an odor of garlic. It is an ingredient of some “fly-powders.” It is present in commercial zinc, iron, sulphuric and hydrochloric acids. It makes a hard alloy with lead, is used in the manufacture of shot, and is often found in Britannia metal. The insolubility of the element as found in these alloys protects us from poisoning by them. Jenkins³ found arsenic to be the cause of the poisoning induced by eating sardines that had been put up in a soldered tin box. The liability of tin and solder to contain arsenic leads to the regulation of the French Commission of Hygiene that tin should not contain more arsenic than 0.01 in 100.⁴

In testing, it appears as a black stain on copper in Reinsch’s test, and as a brown stain on porcelain and a mirror-like ring on glass tubing in Marsh’s test. It oxidizes by exposure to the air, and in that state becomes poisonous. When volatilized by heat, it readily unites with oxygen of the air and forms the poisonous vapor of white arsenic.

Arseniuretted Hydrogen (Chemical Formula, AsH_3 ; Synonyms,

¹ Kobert, *Lehrbuch d. Intoxikationen*, 1902, i, 42.

² Witthaus, *Toxicology*, 1911, p. 413.

³ *Med. Herald*, Louisville, 1882–83, iv, 17.

⁴ Pouchet, *Annales d’Hygiène*, Paris, 1890, 3 S., xxiv, 113.

Arsenic Terhydrid; *Arsin*; *Arsonia*).—This is a gas generated by the action of nascent hydrogen on reducible arsenical compounds. It is colorless, burns an odor of garlic, and burns into water and arsenic trioxid: $2\text{AsH}_3 + \text{O}_6 = \text{As}_2\text{O}_3 + 3\text{H}_2\text{O}$.

The flame is bluish-white or livid, and if a cold body, such as porcelain, is put into it, the metallic arsenic is deposited as a brownish-black spot. The gas, in its course through a small glass tube heated to redness, decomposes and leaves its metallic element condensed on the colder part of the tube as a mirror-like ring. Arsin has a reducing action upon solutions of silver nitrate, causing a black deposit of the metallic silver and liberating arsenous acid. It is the most deadly of the inorganic compounds of arsenic. In addition to the early symptoms—nausea, shivering, dizziness, and prostration—in the severe cases more serious effects appear. There may be jaundice, with dark colored blood, the urine may be bloody and suppressed, and coma may supervene, ending in death. In cases that have been studied many of the red blood-cells are destroyed and the blood coloring-matter is permanently altered and dissolved in the serum. The tissues of the heart, liver, kidneys, and other viscera show fatty degeneration.¹ Wignall²,³ observed that in some cases much more than 0.01 mg. of arsenum can be taken as hydrogen arsenid without fatal results. If the amount inhaled was distinctly toxic it caused feeble pulse, languor, and loss of appetite. The pathology included rapid hemolysis, hematuria, and destruction of renal epithelium and tubules. When treated in a hospital, recovery followed, and after three weeks no more arsenic could be detected in the excreta than the infinitesimal trace misnamed "normal." In a case of inhalation of this gas studied by Delépine⁴ the fatal ending was preceded by hematuria and anuria. The liver contained 0.01 mg. of arsenum per 200 grams of the tissue which was in a state of dropsical degeneration, atrophy, and necrosis. The renal cells showed degeneration and incipient necrosis. On examining 13 workers in a chemical and dye works exposed to the fumes arising when zinc dust is mixed with hydrochloric acid, arsenic was found in the urine of 4, accompanied by albumin in 3, and tube-casts in 2. Recovery from this degree of hydrogen arsenid was complete after four weeks of absence from exposure. Hamilton⁵ reported poisoning by hydrogen arsenid when water acted on ferrosilicon containing 40 to 60 per cent. of silicon. Hydrogen arsenid is liberated from calcium arsenid (Ca_3As_2), present as an impurity.

Arsenic trichlorid (AsCl_3) is a heavy colorless liquid, which boils at 134°C . and vaporizes at lower temperatures. Hydrochloric acid converts part of arsenic trioxid into chlorid and dissolves it. On distilling this solution the arsenic chlorid is found in the distillate. If, however, the arsenic trioxid be oxidized to arsenic acid, hydrochloric

¹ Arsenic Gas Poisoning, John Glaisher, Edinburgh, Livingstone, 1908.

² Wignall, Brit. Med. Jour., 1920, June, 19, 1, 826.

³ Bannister, Ibid., September 25, 1920, 2, 470.

⁴ Jour. Ind. Hyg., 1919, 1, 356.

⁵ Chem. Trade Jour., 1919, 65, 365.

acid will not change that to the volatile chlorid. Both as liquid and as vapor this compound is highly poisonous. Cases have been reported by Legge.¹ The fumes and the dust in the distillation of a mixture of arsenic trioxid, sodium chlorid, and sulphuric acid caused ulceration of the skin and albuminuria with material amounts of arsenic in the urine and hair.

Arsenic Trioxid (Chemical Formula, As_2O_3 ; Synonyms, *Arsenious Oxid*; *Arsenic*; *White Arsenic*; *Ratsbane*).—Besides the above common names for arsenic trioxid, it has another, incorrect, but official, *acidum arsenosum*. It can be obtained as minute octahedral crystals, as a smooth, heavy powder, or as irregular masses looking like translucent glass and white porcelain. The white cake is at first amorphous and semitransparent, and is then called *vitreous*; later, by absorption of moisture, it turns to the white, crystalline, opaque, *porcelain-like* variety which has different solubility. The shops usually dispense it as a heavy white powder, partly amorphous, partly crystalline, prepared from the vitreous variety by grinding. The crystalline "flowers of arsenic" obtained by subliming and condensation are made up of octahedral crystals entirely. Samples of the powder from different packages vary in microscopic appearance, and a specimen may often be identified by the size, luster, and relative proportion of the crystals it contains.² The taste is so faint and lacking in distinctness as to be unnoticed when mixed with food. While it is sparingly soluble in water, and less so in liquid foods, such as milk, beer, coffee, it may easily be suspended in thick soups or incorporated with bread as a solid.

It is extremely unlikely that arsenic can be taken into the stomach in solution and afterward revert to the solid form.³

Owing to the difference in relative amounts of the two forms present in different samples, it is not possible to state the solubility in precise terms, but usually a fluidounce of cold water will dissolve from $\frac{1}{2}$ to $\frac{3}{4}$ grain (about 1 : 1000).⁴ A permanent solution of 16 grains to the fluidounce (about 30 : 1000) can be made by boiling water with it for an hour. In spite of the greater weight (specific gravity 3.699), powdered arsenic has the curious property of floating on water as a white film. By adding hydrochloric or nitric acid, or by making the water alkaline with the hydroxids or carbonates of the alkalis, the arsenic readily dissolves without change of color. White arsenic has no odor, but if heated on charcoal it is reduced to metallic arsenic, which in vapor has an odor of garlic.¹

Physiologic Effects.—In the vast majority of cases the local action of arsenic is pronounced. It does not corrode dead and living tissue alike, as would the corrosive acids and alkalis. Vital irritability is required, or the effect on organic matter will be relatively small. Applied to a part, it irritates so profoundly that the phenomena of inflammation appear at once and make rapid progress to the latest stage of

¹ Chem. Trade Jour., 1919, 65, 385.

² Dana, in the Hayden trial. See Witthaus, Toxicology, 1911, p. 397.

³ Taylor, On Poisons, 1875, p. 318.

⁴ Ibid., p. 287.

local death. It blisters the skin like a burn, and the mucous surfaces respond with equal promptness to its corroding touch. The wide-spread inflammation of the stomach and bowels accounts for numerous cases of rapid death, but the greater number of fatal cases do not exhibit sufficient local mischief to explain the prostration of nervous energy which ends in death. To account for the fatty degeneration of important organs, such as the heart, liver, and kidneys, the theory of Binz and Schulz¹ has been broached. According to them, cell-protoplasm yields oxygen to arsenous acid, converting it into arsenic acid, and later it reverses its action, reducing the arsenic acid. These unwonted activities induce the morbid changes referred to.

Medical Uses.—Arsenic is much used in medicine as a general tonic, given either alone or in combination with remedies of the same class. It has a high reputation in the treatment of skin diseases, especially of pemphigus and psoriasis. Certain nervous affections, as chorea and neuralgia, are often benefited by it. It will frequently prove of service in chronic bronchitis and asthma. In certain kinds of indigestion a small dose taken before meals will improve the appetite, stimulate the gastric and intestinal glands, and so help assimilation as to increase the weight and energies. As a remedy for chronic malarial troubles it has been employed with great success, acting more slowly than quinin, but of more value than the alkaloid in some apparently intractable cases.

The mode of administration usually practised in skin diseases and chorea is to give 5 drops of the *liquor acidi arsenosi* or of *liquor potassii arsenitis* (Fowler's solution), well diluted, after meals, increasing the dose 1 drop daily until the disease is under control or until the eyelids puff and the bowels move too freely, or faint, darting pains are felt in the abdomen. The dose is then reduced to a safer quantity, and persisted in until the warning returns, when it is again reduced. All this time the arsenic pervades all the tissues and can be found in the urine. Occasionally persons are encountered who have an idiosyncrasy for arsenic. Even the minimum dose will produce unpleasant effects. The writer has known cases that would have diarrhea, slight colic, and conjunctivitis after taking 2 drops of Fowler's solution thrice daily for three weeks. A remarkable case of this kind was reported by Nicholson.² After taking in two days 15 minims of *liquor arsenicalis* (B. P.), representing not more than $\frac{1}{6}$ grain of arsenous acid, in doses of 3 minims after meals, an attack of diarrhea came on, an erythema appeared which covered the whole body, and the eyes were reddened. As soon as the arsenic was discontinued the symptoms disappeared.

It sometimes happens that the early warnings are ignored and the arsenic persisted in until permanent injury is done. The form of injury is neuritis causing paralysis, local or complete. Brouardel³ mentions the case of a woman aged twenty-two, under treatment for chronic eczema,

¹ Arch. f. exp. Path. u. Pharm., 1879, xi, 200.

² Lancet, 1893, i, 297.

³ Annales d'Hygiène, 1874, 2 S., 42, 406; see Gaillard, Bull. Soc. méd-lég., 1873-74, 3, 249.

who took 30 drops of Fowler's solution daily for two weeks, and then 40 drops daily for two weeks and three days more. She stopped the doses altogether as the nerves became affected, and in five weeks she was paralyzed.

Symptoms.—If the poison has been in solution and the stomach is empty, the symptoms may appear in eight minutes. If taken solid and with a meal, they may be delayed for as long as ten hours. The usual interval before the first signs is from half an hour to an hour. If a fatal dose has been taken, the symptoms produced are many and various. Departures from the typical forms are frequent, and no symptoms can be considered as characteristic.

In *acute* poisoning, the patient dying within twenty-four hours, the symptoms usually come on within an hour. They are those of a violent irritant producing local inflammation. Added to these, and sometimes occurring independently, are the phenomena of collapse and coma, due to the profound involvement of the central nervous system.

The most conspicuous signs are: (1) An excruciating pain in the pit of the stomach, aggravated by pressure (this burning pain is sometimes absent); (2) sinking sensations and nausea accompany, or may precede, the pain; (3) dry mouth, sore throat, and urgent thirst are common, but may be absent; (4) persistent and forcible vomiting, a sign of an irritability that cannot support the blandest drinks: after ejecting the food, the stomach throws off a rice-water fluid and, later on, a thick mucus, sometimes brown from bile, or sometimes streaked with blood; (5) purging and straining at stools, which may be fetid and bloody, but are apt at first to be thin and watery, like those of cholera morbus (this purging may be absent or insignificant, and in some cases there is obstinate constipation); (6) the urine may be red, bloody, albuminous, scanty, and even suppressed; (7) a feeble, frequent, and irregular pulse ushers in the other symptoms of collapse, the livid and anxious face, sunken eyes, cold and clammy skin; (8) cramps in the calves of the legs, restlessness, spasms ending in unconsciousness. Experiments on cats by Joachimglu¹ show that a marked effect of arsenic is hemolytic jaundice and hemoglobinuria.

A small proportion of the cases are classed as *nervous* or *cerebral* because the central nervous system is prominently affected, while the local irritant symptoms, such as vomiting and purging, are slight or wholly absent. The conspicuous nervous phenomena are great prostration, stupor, convulsions, paralysis, collapse, and death in coma.

Such a case was that of Bolle², to whom was administered, in solution, arsenic afterward estimated to have been not less than 0.388 gram (6 gr.). In about forty-five minutes he had gastric pain and vomiting, and died in three hours. The autopsy revealed no evidence of inflammation in stomach and bowels. From the gastric contents the analyst obtained arsenic trioxid 0.0132 gram ($\frac{1}{4}$ gr.), and from the liver and other viscera, 0.00513 gram (0.078 gr.).

¹ Arch. exp. Path. u. Pharm., 1919, 85, 32-60.

² Casper, J. L., Handbuch der gerichtlichen Medicin, Berlin, 1876, ii, 444.

A *subacute* form is one favored by ingenious criminals, who give the poison in small doses repeated at intervals so as to cause death by gradual prostration through stages relatively slow. The symptoms make their onset later and are less violent than those of the typical acute form. Most of the cases are of this variety: sooner or later there will be loss of appetite, fainting sensations, nausea, dry throat, retching, shooting pains referred to the stomach and intestines, and diarrhea. These merge into vomiting, great abdominal tenderness, tenesmus with bloody stools, scanty and albuminous urine, jaundice, eczema, erythema, pigmentation of skin and keratosis,¹ nervous weakness, feelings of numbness and tingling in the extremities, muscular pains, cramps, paralysis, convulsions, and coma.

Under proper treatment the acute symptoms may subside, and some days or even weeks afterward sequelæ will appear. These are attributable to a chronic inflammation of the peripheral nerves, ending in degeneration of the fibers extending from the periphery toward the center, causing loss of sensibility and paralysis in the hands or feet, which may progress until the muscles waste and give the electric response known as the reaction of degeneration. This consequent paralysis was shown in a case reported by Holst.² The poisonous dose was a tablespoonful of Paris green. During the first twenty-four hours there was no disturbance of the digestive organs except vomiting and slight abdominal pains. After eight days there appeared a rapidly progressing weakness in the lower limbs. After six weeks examination showed complete anesthesia and paralysis of the lower extremities, with muscular atrophy and partial loss of sensibility and motion in the upper limbs. The degeneration reaction was elicited from all four extremities. The knee-jerk had gone, but bladder and rectum were unaffected. Gradual recovery followed the treatment by baths, nourishing diet, and potassium iodid. Like interesting features are to be found in a case reported by Kovacs.³ A man took at least $2\frac{1}{2}$ drams (9.72 gm.) of arsenic trioxid. The acute symptoms of gastro-intestinal irritation were controlled by treatment, but a week later an affection of the peripheral nerves developed. First there appeared edema of both legs, and a week later anesthesia of the feet, shooting pains, and unsteady gait. Anesthesia began at the fingers and invaded the arms. Some muscles in all the extremities wasted and showed fibrillary twitchings. The knee-jerk and the superficial reflexes were lost. In four weeks of treatment the ataxia disappeared and the muscles grew firm, the pains and the paresthesia proving the most intractable symptoms.

Anomalous Cases.—Emphasis should be placed upon the statement made above, that no symptoms can be considered characteristic. Fatal cases have been reported which presented typical postmortem appearances, and yet during life exhibited no pain, vomiting, or purging, and in which thirst was not marked in degree.

¹ See Stockman, *Edinb. Med. Jour.*, 1921, 27, 1.

² *London Med. Record*, 1887, xv, 119; *Proc. Riga Med. Soc.*, 1885, p. 373.

³ *Wien. klin. Wochenschr.*, 1889, ii, 649.

Fatal Dose.—Two grains is the smallest fatal dose of white arsenic yet reported.^{1, 2, 3} Suicide was accomplished in the case of a woman who had recently aborted by taking $\frac{1}{2}$ fluidounce of Fowler's solution, equal to 2 grains of arsenic trioxid, in broken doses within four days.⁴

Fährenhorst⁵ reported a death in six hours from $4\frac{1}{2}$ grains in solution given by mistake to a boy of four years. His symptoms were spasms of the gullet, retching, vomiting, burning in the pharynx, cutting abdominal pains, cramps, trembling, great prostration, collapse, and death. Two weeks after death the autopsy revealed gastritis, duodenitis, laryngitis, pharyngitis, and congestion of the lungs. After cultivating a "tolerance" for arsenic in himself Harding⁶ found $1\frac{1}{2}$ grains (0.08 gm.) of white arsenic unendurably toxic.

After careful search through the literature of the subject Witthaus⁷ states that he has failed to find "any record of the clearly established death of an adult from a single dose of less than 2 grams (30 gr.) of arsenic in the solid form." This dose, taken by a woman of twenty-seven years,⁸ caused characteristic symptoms ending by death in twenty-six hours.

To reach this conclusion one must ignore those estimates of dosage not based on exact weight, insist upon the absolute health of the subject at the time of administration, and eliminate cases which show in the autopsy any other lesions than those typical of arsenic. Until these extraordinary conditions are fulfilled we must depend for precision of determination as to the minimal lethal dose upon experiments on the lower animals. Fortunately, we are not without significant data of this kind. Rouyer⁹ found that the absorption, by dogs, of 0.0025 gram (calculated as As.) per kilo (0.018 gr. per pound) sometimes, and of 0.003 gram (calculated as As.) per kilo (0.021 gr. per pound) always caused death. Making the usual allowance for body weight, this puts the fatal dose for a man of 150 pounds at 0.17 to 0.20 gram (2.7–3.15 gr.). These results coincide so perfectly with the careful inferences made by the best authorities (Huseman, Kobert, and others^{10, 11}) that they may well be considered as justifying the conclusion that 3 grains of absorbed arsenic would probably prove fatal to an average man.

Recovery is possible after much larger quantities, as the symptoms vary according to the bodily condition of the person, the state of the

¹ Taylor, On Poisons, 3d ed., 1875, p. 302.

² Wormley, Micro-Chemistry of Poisons, 1885, p. 246.

³ Mann, Forensic Medicine and Toxicology, 1893, p. 431.

⁴ Castle, Prov. Med. and Surg. Jour., 1848, p. 347.

⁵ Mag. f. d. ges. Heilk., 1852, 20, 483.

⁶ London Lancet, 1914, i, 288.

⁷ Witthaus and Becker, Medical Jurisprudence, Forensic Medicine, and Toxicology, 2d ed., 1911, iv, 439.

⁸ S. M. Ward, Therap. Gazette, 1885, 3 S., i, 519.

⁹ Thèse de Nancy, 1875. See, also, Rouyer and Feltz, Gaz. d. hop. Paris Méd., 1875-76, i, 962.

¹⁰ Husemann, Handbuch der Toxikologie, 1862, p. 819.

¹¹ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, ii, 251; also Blyth, Poisons, Effects and Detection, 4th ed., 1906, p. 557; Falck, Lehrbuch der prak. Toxikologie, 1880, p. 93; Guy and Ferrier, Principles of Forensic Medicine, 7th ed., 1895, p. 534; Tardieu, Etude Médico-légale, 2d ed., 1875, p. 353.

stomach, and the form of the poison. Remarkable recovery may ensue if the poison is taken in lumps,¹ or if vomiting evacuates the stomach before absorption has set in.

Fatal Period.—Taylor² states the shortest interval before death as twenty minutes. A large dose may overwhelm the entire nervous system so as to bring about collapse and coma within the hour. The average period is about twenty-four hours. In the subacute cases the fatal termination may not occur for several weeks. In one reported by St. George³ it was delayed for over three months. A man of sixty-eight years took by mistake for magnesia a heaping teaspoonful (180 gr.) of arsenic trioxid in hot milk followed by a supper of porridge and milk. Some hours after began the characteristic violent and persistent vomiting, purging, abdominal pain, leg cramps, prostration, and anuria. In a few days recovery from gastro-enteritis seemed complete, but poisoning of nerve tissue set in. Pain, numbness, and paralysis invaded arms, hands, legs, and feet. Ataxic gait and lost knee-jerk preceded a slowly ascending paralysis which ended in hypostatic pneumonia and death. For the whole period arsenic was present in the urine.

Treatment.—The first indication is to *evacuate the stomach* by administering an emetic mixture of a teaspoonful of mustard and a tablespoonful of salt in a tumbler of warm water. This may be repeated in ten minutes, or a hypodermic injection of apomorphin or an emetic dose of sulphate of zinc can be given. Where criminal poisoning is suspected, tartar emetic should be avoided, as it will make detection of arsenic more difficult. The stomach-tube will prove valuable if the stomach is not full of mixed food, pieces of which would occlude the openings in the tube. If feasible, the stomach washings should be copious and frequently repeated. Large drafts of hot milk and water will facilitate the washing out of the poison. At the same time the antidote may be given to make the residua insoluble and inert. For this purpose reliance has been placed on teaspoonful doses of dialyzed iron or on the freshly made *moist ferric hydroxid*, to convert the arsenic trioxid into ferric arsenate, which is only very sparingly soluble. In the official preparation, Ferri Hydroxidum cum Magnesii Oxido U. S. P., two antidotes are combined. This may be prepared extemporaneously by diluting $\frac{1}{2}$ ounce of *tinctura ferri chloridi* with a tumbler of water and adding magnesia in excess. The whole mixture may be taken without straining and repeated several times. If the ferric hydroxid is prepared by adding ammonia-water to ferric sulphate or ferric chlorid, then the gelatinous precipitate should be separated from the excess of ammonia by straining through a handkerchief or piece of cheese-cloth. To clear the intestine a dose of castor oil should be given. It is still an open question whether this antidote is efficient, so that investigations are at present under way to determine this point.

¹ H. C. Wood, *Therapeutics*, etc., 1874, p. 320; Joachimoglu, *Klin. Wehnschr.*, 1922, 1, 169.

² Taylor, *On Poisons*, 1875, p. 303.

³ *Brit. Med. Jour.*, 1921, 1, 192.

It must be remembered, in this connection, that free gastric lavage must follow the administration of the antidote. Just how long a period may elapse before the antidote becomes absolutely inefficient remains to be determined. In spite of evacuants and antidote it sometimes happens that the poison in the form of a powder adheres unchanged to the folds of the mucous membrane. Sieber¹ has tried the effect of magnesium sulphate on animals poisoned with organic arsenicals, but his results were not convincing. Hansen,² in his work with this treatment, believes more investigation is necessary.

Postmortem Appearances.—Putrefactive change is usually retarded when the body is permeated with arsenic. If the dose has been large and life prolonged until absorption could take place, this preservative effect will often keep the viscera free from gases and putrid odors for as long as seventeen months. A smaller dose, especially if rapidly followed by death before general diffusion could occur, would not have the same action. The pathologic changes induced are usually those of gastroenteritis common to the class of local irritants of the stomach and bowels, and if the patient should survive for a number of hours, the absorbed poison will set up fatty degeneration of the heart, liver, and kidneys.

Mouth, Pharynx, and Esophagus.—The repeated acts of vomiting bring the poison up from the stomach more or less dissolved and active. Inflammatory change sets in at once, and the upper part of the alimentary tract will present enlarged vessels, reddened patches, and erosions.

Stomach.—The lining membrane of the stomach may be covered with a tough mucus or lymph in which white particles of the poison will be embedded, or, if Paris green has been taken, there may be patches of a bright green color. Sometimes the arsenic penetrating the gastric walls as far as the peritoneum has been turned into yellow sulphid by the reaction with hydrogen sulphid of putrefaction (see Plate 2). The mucus itself may be abundant and dark, containing blood. Small dark red dots of effused blood, looking like flea-bites, may stud the surface of the membrane, itself a paler red, obviously due to diffused inflammation. Upon the prominent folds of the mucous membrane these effusions may run together in well-marked streaks of dark red color. The inflammation may involve the other coats of the stomach, and all of them be found thickened and corrugated. Occasionally localized gangrene ensues. Rarely does the inflammation progress to ulceration, and still more rarely does the ulcer involve the whole structure, causing perforation.

While some degree of gastric inflammation will nearly always be found, it is important to note that death may occur from the cerebral effects ending in coma, while the mischief done to the stomach may be insignificant. If the body has been embalmed with formaldehyd before the organs are removed for examination, practically no macroscopic signs of inflammation will be noted.

Intestines.—If death be delayed for several days, the whole length of the intestinal tract may be inflamed, but usually the small intestine,

¹ Arch. Int. Pharmacol., 1912, p. 22.

² Jour. Pharm. and Exp. Therap., 1921, xvii, 105.



STOMACH FROM A CASE OF ACUTE ARSENICAL POISONING (VON HOFMANN).

A woman aged twenty-nine years was poisoned with arsenic. On May 27th she was first taken with vomiting and diarrhea, eventuating in death on June 4th. Though there had been seven days' profuse vomiting and diarrhea, a considerable quantity of arsenic was found in the dead body. She had no systematic medical attention. The necropsy showed a flabby, yellowish, and dilated heart, with cloudy swelling of the muscular fibers. Both the liver and kidneys were the seats of parenchymatous degeneration.

The stomach was moderately distended with a watery, turbid, bloody fluid. The inner wall was markedly swelled, softened, and congested. On the crests of the rugae were ecchymotic points closely set, and mixed with them were injected vessels. At the middle of the greater curvature were dark red, circumscribed areas of confluent ecchymoses denuded of epithelium. Upon and around these areas was a fine, smooth, bright yellow deposit. The intestines contained a large quantity of watery, turbid fluid resembling rice-water. The mucous membrane was pale violet in color and minutely injected. Its epithelium was loose and easily separated.

and more frequently the duodenum, alone will be involved. There is diffused redness, with scattered patches of a deeper hue, and the contents may be bloody, or perhaps yellow from the formation of yellow sulphid. Like the stomach, the intestines may show little or no sign of inflammation, even with the arsenic present in considerable amount, the death being due to the effect on the central nervous system.

Changes in remote parts may occur if life be prolonged for a number of hours, and are most conspicuous in the *heart, liver, and kidneys*. Any or all of these may show fatty degeneration. The heart is the seat of effusions of blood under the endocardium, especially of the left ventricle.

Chronic Poisoning.—Peculiar features are found in chronic poisoning that have given rise to the theory that arsenic is *cumulative*. Careful investigation shows that the poison is not stored up in the tissues for such a length of time as are lead and mercury, though the effects appear to accumulate in force and gravity.

Arsenic is readily diffusible, and, passing to the tissues, abides for a few weeks and then is eliminated. The dose may be considerable, yet if the patient lives for three weeks, the arsenic may have entirely disappeared from the soft tissues, but, as Brouardel and Pouchet found, it may still be detected in the bones. On the other hand, cases are recorded where the poison has been found in the liver and bones after two and even six months. In medical practice it is customary to give Fowler's solution in gradually increasing doses until the limit of tolerance is reached, denoted by the appearance of puffed eyelids and loose bowels. The dose is then reduced progressively. If the full dose is persisted in, the symptoms of chronic poisoning supervene.

The poison has been known to enter by many avenues—inhaled by the lungs, swallowed in food or as excessive medication, applied to the skin by mistake in cosmetics or in the red dye of socks and gloves. The person falls into "poor health," losing appetite and all desire for exertion. Soon twinges of pain, especially sudden colic, will appear. Complaint is made of "sickness" and faintness. The eyelids puff, the conjunctiva is reddened, and the eyes become very sensitive to light. Such signs of indigestion as occasional vomiting, colic, and chronic diarrhea arise. The color fades from the face, the complexion becoming waxy. The person is said to have a wasting fever. Progressive weakness and loss of weight prevail throughout. The hair becomes dry and may fall out, and the nails are brittle and loose. The skin may exfoliate or show spots of darker hue, with eruptions of eczema or erythema. The mouth may lose patches of mucous membrane, form ulcers, and show the symptoms of salivation. The throat, nose, larynx, and bronchial tubes may be affected with a catarrh, causing cough, bloody expectoration, aphonia, and copious coryza. At a later period the nerve-fibers become inflamed and degeneration of this structure is a consequence. At first the sensory nerves indicate the mischief going on by attacks of numbness and tingling in the extremities, which are followed eventually by total absence of normal sensation, or, it may be, by pain and tenderness. When the motor nerves of the hands and feet are in-

volved, there are loss of power in them and wasting of the affected muscles. Even if the poison is discontinued, the paralysis usually lasts for many months, recovery being very slow and generally incomplete. The paralysis may extend until it is general, and death ensue from failure of the heart due to fatty degeneration. A horny condition of the palms and soles, or keratosis, may be produced by the long-continued use of arsenic as a remedy in chronic psoriasis.¹

In most of the Rocky Mountain copper-ore smelting works, arsenic trioxid is a valued by-product. Its dust is breathed daily by many workers, who frequently suffer a characteristic perforation of the nasal septum and related pathologic conditions of the skin of the face and eyelids with conjunctivitis and laryngitis.^{2, 3, 4}

Arsenical Applications.—Deaths have been recorded from applications of arsenic, with homicidal intent, to the rectum⁵ and the vagina. It has poisoned when used as a urethral injection.

Haberda has reported a case⁶ of suicide by means of arsenic contained in a paper bag inserted into the vagina. Incidentally, he referred to the instances of a person who murdered 3 of his wives successively by introducing arsenic into the vagina after connection; of a single woman who, finding herself pregnant, attempted to produce abortion by this means, but killed herself thereby; of a prostitute murdered by a man who introduced a quantity of arsenic into the vagina, wrapped up in a knot of horsehair.

In these cases of absorption from mucous surfaces and also when applied to the unbroken skin, as ointment, lotion, or powder, the symptoms are much the same as when taken by the mouth. There is, first, a local inflammation, soon followed by nausea, vomiting, thirst, pain, diarrhea, suppressed urine, and nervous symptoms.

An arsenical ointment applied to the scalp of a child to cure an eruption caused death in ten days, with symptoms of gastro-enteritis. The postmortem appearances were redness and inflammation of the stomach and bowels, and the poison was detected in the gastric contents and the liver. By mistake white arsenic was dispensed for a dusting-powder to the skin, with fatal consequences to 17 children.⁷ Arsenical plasters used to remove tumors have had severe systemic effects, and even death has been caused by them.⁸ In such cases the poison has been found to be distributed throughout the body.

Arsenic-eating.—In view of the deadly nature of this poison, it is not surprising that toxicologists were for a long time skeptical as to the possibility of creating a tolerance for arsenic. It has been proved indu-

¹ Hutchinson, *Archives of Surgery*, 1895, vi, 186; see also *ibid.*, 1893, 1894, v, 339. Other cases have been reported in the same journal (vol. v) showing that the corns and other similar growths after years of use of arsenic tend to take on malignant action and become epithelial cancer.

² Kober and Hanson, *Dis. of Occupation, etc.*, 1916.

³ Davis, *Jour. Amer. Med. Assoc.*, June 2, 1917, 68, 1620.

⁴ Dunlap, *ibid.*, February 26, 1921, 76, 568.

⁵ Foderé, *Méd. légale*, 1813, iv, 266.

⁶ *Wien. klin. Wchnschr.*, 1897, x, 201.

⁷ Woodman and Tidy, *Hand-Book of Forensic Medicine and Toxicology*, 1877. See also Tidy, *Lancet*, 1878, 2, 250; *Brit. Med. Jour.*, 1878, i, 795.

⁸ Tardieu, *Etude Médico-Légale sur l'Empoisonnement*, Paris, 1867.

bitably that in Styria, Lower Austria, and India individuals have been found who, by carefully increasing the dose at long intervals, have accustomed themselves to take with impunity what in others would produce poisonous symptoms.

These arsenic-eaters take for twenty or thirty years from $\frac{1}{2}$ to 2 grains or even more of arsenic trioxid at intervals of once a week or oftener, with the intent to increase their powers of endurance. The persons examined have been robust men who lead an active mountain-climbing life. It is not unlikely that to a high constitutional power of resistance they add an unusual activity of the excretory organs. They appear to be especially liable to sudden death. Joachimoglu¹ is skeptical toward these assertions of perfect tolerance and general cellular immunity. Hoarseness and catarrh of the respiratory tract are wide-spread among the arsenic eaters.² Cloetta³ attributed a degree of developed tolerance to a diminished absorption owing to changes in the alimentary mucosa making it less permeable to arsenic trioxid. Joachimoglu⁴ held that in persistent feeding with arsenic trioxid there is a gradual recovery of the mucosa from the catarrhal condition first induced, so that it is more resistant to the irritant as well as less absorbent of the rather insoluble poison. Schwartze⁵ shows that the toxicity of different preparations of arsenous oxid varies according to the coarseness or fineness of their subdivision, the action being dependent on varying solubility.

Popular writers have helped to create the impression that there are village communities who indulge themselves in arsenic as others do in tobacco. This is not well founded, nor is there evidence to support the opinion that moderate arsenic taking is common among Americans who wish to improve their complexion. Among its transient pathologic effects are a clear pallor, sometimes a circumscribed flushing of the cheeks, and a glistening of the eye. These soon pass into a waxy skin and puffy eyelids—anything but pleasing to look upon. Very rarely it happens that a person for whom Fowler's solution has been prescribed will take it of his own volition to restore his health, but a persistence in the habit is soon found to be prejudicial and the dose given up. Physicians consider it doubtful if any considerable number of persons find it compatible with comfort for more than a brief period. Harding⁶ began with $\frac{1}{80}$ grain (0.001 gm.) of arsenic trioxid thrice daily after meals and gradually increased the dose to $1\frac{1}{5}$ grains (0.08 gm.), which he found unendurably toxic. Even 1 grain (0.065 gm.) doses could only be taken with dry food-stuffs. With soups or beverages at the meal it caused immediate pain in the abdomen and later looseness of the bowels.

In trials for arsenical poisoning the defense sometimes broaches the theory of arsenic-eating to account for the arsenic found in the body.

¹ Arch. f. exper. Path. u. Pharm., 1916, 29, 419.

² Von Tschudi, Wien. med. Woch., 1853, 3, 6.

³ Arch. f. exper. Path. u. Pharm., 1906, 54, 196.

⁴ Loc. cit.

⁵ Jour. Pharm. and Exp. Therap., 1922, 19, 258; Ibid., 20, 181.

⁶ London Lancet, 1914, 1, 288.

A celebrated instance was the case of Mrs. Maybrick, convicted of poisoning her husband at Liverpool, England, in 1889.¹ The symptoms were diagnosed by the physicians two days before death as the result of a succession of arsenic doses given within two weeks. The husband of the accused, after tea on April 27th, had an attack of vomiting. On April 28th the vomiting continued and the lower extremities were stiff. After lunch on May 1st and for three days thereafter he was again sick and retching. A week later the vomiting had not left him, his throat was dry and sore, and his bowels were very loose. A diarrhea with straining at stool was marked on May 8th, worse on May 9th, and death ensued on May 11th.

The postmortem appearances corresponded with the symptoms, and arsenic in small amount was found in the liver and intestines. Among the effects of Mrs. Maybrick were found packages of arsenical rat-poison, white arsenic, and arsenical fly-papers. The list of things about the house found to contain arsenic numbered fourteen. She asserted that she made extracts of the fly-papers for use with the various other forms of arsenic as cosmetics. Having been seen to put something secretly into the bottle of beef-extract used by her husband, found afterward to contain arsenic, she stated in her defense that at his request she put in a white powder he was in the habit of using. A colored servant testified that years before, Mr. Maybrick would put arsenic into his beef-tea. It was shown that the accused was on bad terms with her husband and was carrying on a liaison previous to and at the time of his death. Under the instructions of the court the jury discredited the story of arsenic-habit, found her explanations unsatisfactory, and convicted her of the poisoning.

Tests in the Solid Form.—When undissolved, it is easy to recognize the poison by heating it in a sublimation tube and applying other tests to the deposited vapor.

1. **Sublimation Test.**—Arsenic trioxid sublimes without fusing at a temperature lower than 218° C. (424° F.), the sublimate under a lens presenting octahedra and modified forms, such as tetrahedra and dodecahedra (Fig. 31, c).

Fallacies.—The octahedral form distinguishes the minute arsenical crystals from other volatile white solids subliming at this temperature, such as corrosive sublimate, calomel, and oxalic acid. While many authorities assert that the sublimate of antimony oxid is always amorphous, according to Wormley, Witthaus, and others it may sometimes occur as octahedral crystals like arsenic.

2. **Reduction Test.**—This test is applied to any solid compound of arsenic, including Paris green, the two sulphids, and any arsenite. The dry substance is introduced into a reduction tube, part of which has been drawn out to a small caliber at the bottom. It is covered with six times the quantity of a well-dried mixture of 3 parts of sodium carbonate to 1 part of potassium cyanid. Heated gently, some moisture may first appear on the tube. This can be removed

¹Stevenson, Guy's Hosp. Rep., 1889, 3 S., xxxi, 307.

with a spiral of filter-paper, a swab of absorbent cotton, or by gently heating the moist glass. When the tube is dry, apply strong heat to the flux and then to the arsenic. The arsenical compound is reduced to metallic arsenic, which is deposited higher up on the tube as a mirror-like ring, black shading to brown or gray (Fig. 31, *a* and *b*).

Fallacies.—The compounds of antimony yield no mirror with this flux, but the compounds of mercury, cadmium, tellurium, and selenium may. When viewed by a lens, the mercury mirror is found to have a fringe of globules. To distinguish the arsenical mirror, the end of the tube must be broken off and the ring heated with the tube aslant. The air playing over the hot arsenic will oxidize it, and the mirror will be vaporized and appear on the cooler parts of the tube as minute white crystals of arsenic trioxid, octahedral in form (Fig. 31, *c*). If another

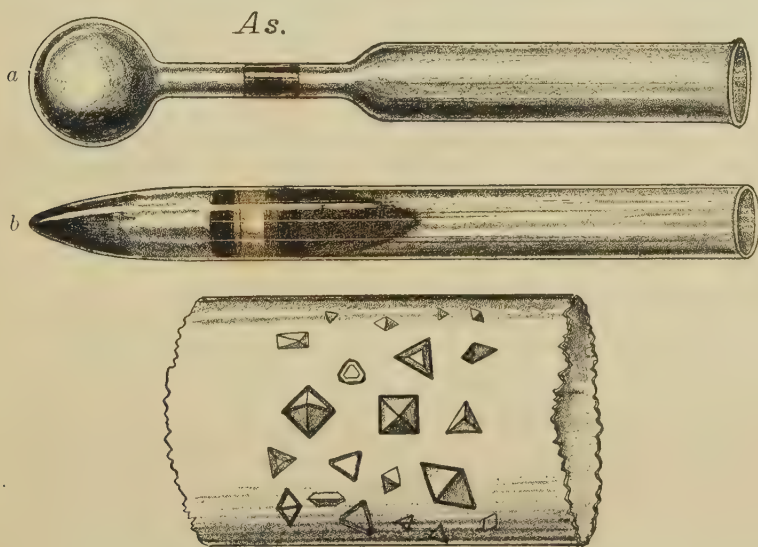


FIG. 31.—*a* and *b* are two reduction tubes showing arsenical mirror after reduction test; *c*, octahedra of As_2O_3 sublimate, magnified.

specimen is treated with a warm solution of chlorinated lime, the mirror will dissolve in a manner characteristic of arsenic.

Delicacy.—If $\frac{1}{1000}$ grain of arsenic be tested in a tube contracted to $\frac{1}{20}$ inch in diameter, it yields a visible sublimate which will resublime and show many crystals of arsenic trioxid.¹

Tests in Simple Solutions.—When the poison has been obtained in solution free from organic or other matter, the following tests will help to identify it:

1. **Ammoniosulphate of Copper Test.**—Enough of the reagents for the test can be freshly made by putting about 5 drops of ammonium hydroxid in a test-tube and diluting it with 10 c.c. (3 fluidrams) of water. To this dilute ammonia-water a weak solution of copper sul-

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 259.

phate is added until the bluish-white precipitate ceases to dissolve. The slight excess of cupric hydroxid should be removed by filtration. The clear blue solution added to a solution of arsenic trioxid will throw down a bright green precipitate of cupric arsenite— CuHAsO_3 (Scheele's green) (No. 2, Plate 3). A portion treated with ammonium hydroxid dissolves as a clear blue liquid; another portion will make a colorless solution with nitric acid.

Fallacies.—While no metal but arsenic yields the green precipitate, different organic substances give a green color, and, therefore, interfere with it. The arsenic precipitate, when dried and subjected to the *reduction test*, will give the metallic mirror. Dissolved in hydrochloric acid and subjected to Reinsch's test, the metal deposit will show on copper-foil.

Delicacy.—A green response has been obtained from $\frac{1}{100000}$ grain of arsenic.¹

2. Ammonionitrate of Silver Test.—To prepare the reagent, freshly dilute some ammonium hydroxid, as stated in the last test, and add to it a strong solution of silver nitrate until the precipitate of silver oxid formed ceases to dissolve. This reagent yields with solutions of arsenic trioxid a canary-yellow precipitate of silver arsenite, Ag_3AsO_3 (No. 3, Plate 3), which dissolves in ammonium hydroxid and in nitric acid, but not in sodium hydroxid. If dried and heated with flux, as in the reduction test, silver arsenite will be identified by the metallic mirror formed on the cooler part of the tube.

Fallacies.—Other chemicals, such as phosphoric acid, the alkaline iodids, and bromids, will give a like yellow precipitate.

Interferences.—The chlorids, hydrochloric acid, and organic matter decompose the reagent and interfere with this test.

Delicacy.—Minute yellow flakes are yielded by $\frac{1}{100000}$ grain.²

3. Bettendorff's Test.—A freshly made solution of stannous chlorid is added to the suspected material dissolved in strong hydrochloric acid. Having immersed a small piece of pure tin-foil, the mixture is heated; if arsenic is present, a brown color or a grayish-brown precipitate of the metal is formed.

Delicacy.—A brown coloration is yielded by $\frac{1}{100000}$ grain, forming $\frac{1}{500000}$ of the hydrochloric acid mixture.³

Tests in Complex Solutions.—To detect the arsenic in solutions with other matters the following tests are useful:

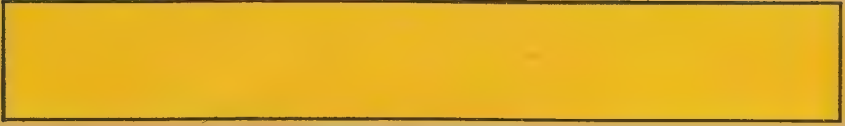
1. Hydrogen Sulphid and Hydrochloric Acid Test.—If the solution, acidified with hydrochloric acid and warmed, be subjected to a current of well-washed hydrogen sulphid, bright yellow arsenic sulphid, As_2S_3 (No. 1, Plate 3), will be thrown down. This deposit is insoluble in cold hydrochloric acid, but hot nitric acid decomposes it and forms solution of arsenic acid. It will dissolve in the alkalis and in ammonium sulphid.

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 264.

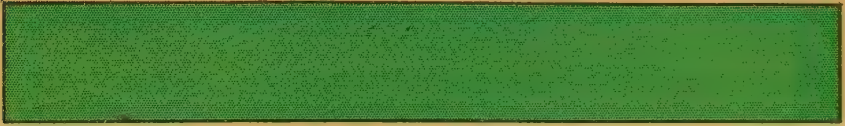
² Wormley, *Ibid.*, 1885, p. 262.

³ Wormley, *Ibid.*, 1885, p. 296.

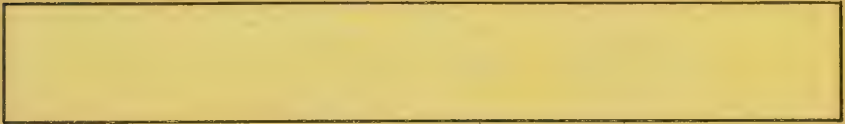
PLATE 3.



Arsenous sulphid produced in hydrogen sulphid and hydrochloric acid test for arsenic.



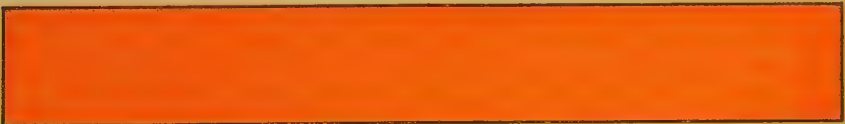
Cupric arsenite produced in ammonio-sulphate of copper test for arsenic.



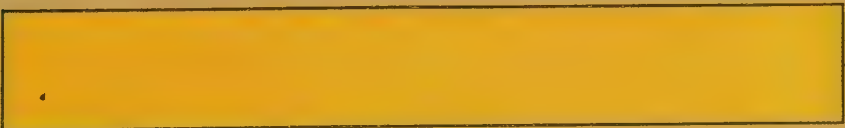
Silver arsenite produced in ammonio-nitrate of silver test for arsenic.



Silver arsenate produced in arsenic solutions by treatment with silver nitrate.



Antimonous sulphid produced in hydrogen sulphid test for antimony.



Stannic sulphid produced in hydrogen sulphid test for stannic compounds.

Fallacies.—Yellow or orange precipitates may occur from cadmium, antimony, and tin, and by the possible separation of sulphur from the hydrogen sulphid. To verify the nature of the precipitate, it should be separated by filtration, dissolved in ammonia, evaporated to dryness, and subjected to the *reduction test* and the resubliming of the metallic mirror to octahedral crystals.

Delicacy.—A yellow turbidity, ending in a good deposit, has been obtained from $\frac{1}{100000}$ grain.¹

2. Gutzeit's Test.—In a test-tube containing 1 c.c. of the suspected solution, either acid or neutral, put about 1 gram of chemically pure zinc and 5 c.c. of a 6 per cent. dilution of sulphuric acid. In the upper part of the tube insert a plug of absorbent cotton moistened with lead acetate, and clasp over the mouth of the tube a cap made of three layers of filter-paper. Having wet only the upper layer with a drop of saturated solution of silver nitrate, set aside in a dark box for a time. Arsenic will cause on the paper a bright yellow spot, which darkens by separation of metallic silver when water is applied to it. The color made by antimony is at no time yellow, but is at once brown or black.

3. Reinsch's Test.²—The purity of the materials for this test may be established by a blank experiment. A few slips of bright copper-foil should be put into pure water containing one-sixth part of hydrochloric acid, and then heat applied so as to boil for five minutes. The copper remaining bright, the hydrochloric acid may be assumed to be pure; but every detail of this test and others must be paralleled by blank experiments.³ Having added one-sixth volume of hydrochloric acid to the solution to be tested, a strip of pure copper-foil is put into it and the whole boiled for a few minutes. If arsenic be present as arsenous acid or arsenites, it is deposited as a dark film, purple to steel-gray in color. From *arsenic acid* it is deposited only when the solutions are strong. Many of the organic arsenicals do not give this test without previous oxidation.

Fallacies.—A coating will be left on the copper by arsenic, antimony, mercury, bismuth, gold, and platinum; even prolonged boiling in hydro-



FIG. 32.—Apparatus for Gutzeit's test for arsenic.

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 265.

² Das Arsenik, Nürnberg, 1843; consult also section on General Principles of Toxicology, p. 50. See also Jamieson, *Jour. S. African Assoc. Anal. Chem.*, 1921, 4, 9; *Chem. Abs.*, 1921, 15, 3430.

³ As ordinary copper itself may contain arsenic, it should be tested by first giving it a polished surface and then dropping a sample into a boiling mixture of equal parts of solution of chlorid of iron and pure strong hydrochloric acid. If impure, arsenic will show as a black coating.

chloric acid may tarnish it. To verify the arsenical film, the copper slip should be washed in alcohol and ether, dried with filter-paper, rolled into a cylinder, and inserted into a hard-glass tube open at both ends, all by means of forceps, the finger not touching the foil. When the heat of a spirit-lamp is applied, the metallic film sublimes and is deposited on the tube as a white ring of octahedral crystals of arsenic trioxid, which will dissolve in water and respond to ammonionitrate of silver and the other tests given above.

Besides arsenic, there are two other metals, antimony and mercury, which make a sublimate under these conditions. Mercury makes a sublimate of shining globules (Fig. 30, p. 195); the antimony sublimate is generally amorphous, but may be in octahedral crystals or needles.

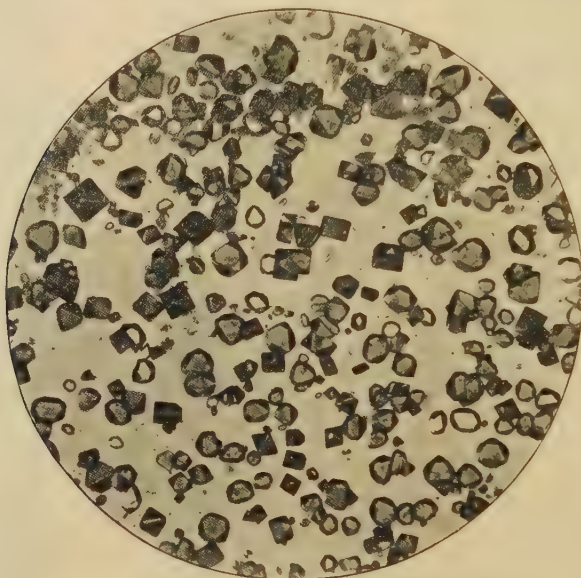


FIG. 33.—Sublimate of arsenic trioxid (magnified 340 diameters).

To establish the arsenical nature of the sublimate, the octahedral crystals must be well defined. In order to get the crystals deposited on a glass slide convenient for the use of a $\frac{1}{4}$ -inch objective, the following manipulations will be useful¹: Having obtained the arsenic stain on copper-foil, the foil is removed, washed, and dried without contact with the fingers, and cut into narrow strips. A subliming tube should be made of thin glass, diameter $\frac{1}{4}$ inch, length $1\frac{3}{8}$, sealed at one end, and a lip turned back at the other open end, so that it will hold when hung in an opening made in a sheet of brass 4 inches by 2. The sheet of brass should be laid upon the ring of a retort-stand, with the tube suspended, and then the tube warmed so as to dry it. After

¹ Report of Committee of National Health Society, Brit. Med. Jour., 1883, i, 1220.

cooling, the tube receives the strips, and a microscope slide, dried by heat, is placed upon it. The glass subliming tube should then be heated, so as to permit the flame to play also on the bottom of the brass plate. A whitish sublimate will appear on the glass slide in a few seconds, but the heat should not be withdrawn until the white patch begins to clear up at the edges and has a diameter of $\frac{1}{4}$ inch. The cold slide examined by a $\frac{1}{4}$ or $\frac{1}{8}$ inch objective will show minute octahedra and tetrahedra, and modifications of these (Fig. 33).

Interferences.—This test does not work properly if nitric acid, a chlorate, manganese dioxid, or other oxidizing agent is present. They cause the solution of the copper and prevent the formation of an arsenical coating. With this simple and delicate test it is possible for the physician to make an early diagnosis during life, by examining the vomited matters or urine without any other preparation of the materials

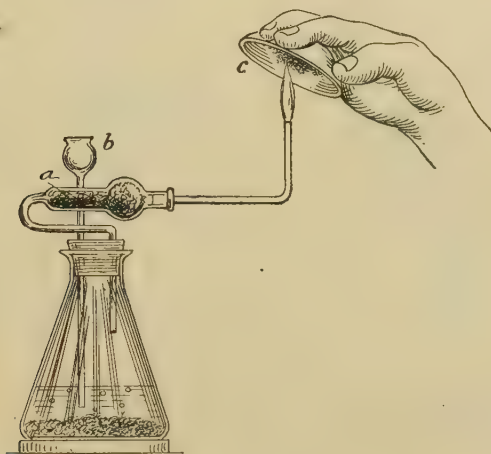


FIG. 34.—Marsh's apparatus for the detection of arsenic.

than digestion on the water-bath with one part of *pure* hydrochloric acid to six of the tested fluid. The copper slips can then be boiled in this fluid. Any marked darkening of the copper is significant usually of arsenic, antimony, or mercury.

Delicacy.—With ordinary reduction tubes, distinct octahedra form when only $\frac{1}{100000}$ grain of arsenic is present; with great care, using very fine tubes, $\frac{1}{500000}$ grain has been revealed.¹

4. **Marsh's Test.**—When hydrogen is generated in the presence of compounds of arsenic, they give up the arsenic, which, uniting with it, forms arsenic terhydrid or arsenuretted hydrogen. This is a gas which, by heat, yields the metallic arsenic for identification by tests already stated. In a flask arranged for generating hydrogen (Fig. 34), with air-tight connections, pure zinc is placed, and pure cold dilute sulphuric acid (one part to six of water) is added to it through the

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 274.

funnel-tube (b). The gas is first conducted through a drying-tube containing calcium chlorid (a) between plugs of glass wool, and then through an exit-tube of hard glass, about 5 mm. ($\frac{3}{16}$ in.) internal diameter, and 25 to 50 cm. (10–20 in.) long, which is turned up at the end and drawn out at the tip to make a jet.¹ After waiting a few minutes for the air in the apparatus to escape a Bunsen flame is applied in the course of the exit-tube which is heated red hot, and if no stain appears on the glass after fifteen minutes the chemicals may be considered pure. The gas-jet should be ignited, and if arsenical fluid is now poured in by the funnel-tube in small portions the pale hydrogen jet becomes more luminous and livid in color. If organic matter should cause

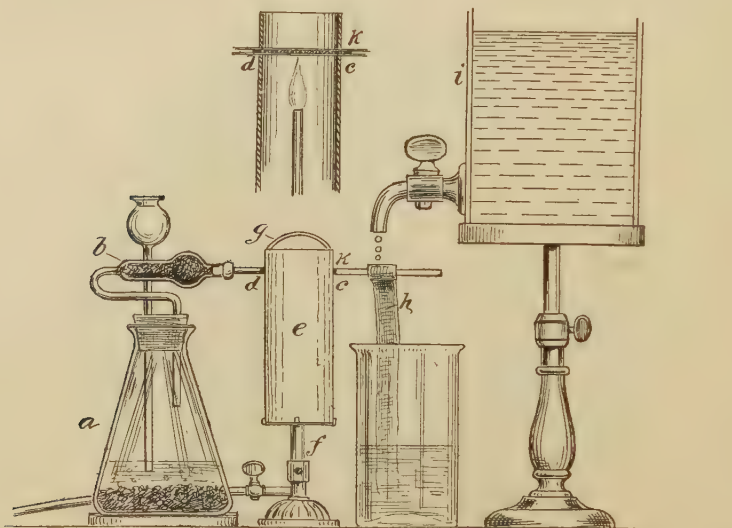


FIG. 35.—Modification of Marsh's apparatus to secure the most delicate results: *a*, Generating bottle; *b*, calcium chlorid tube; *c*, point where hard-glass tube narrows from $\frac{1}{2}$ to $\frac{1}{8}$ inch, a small plug of asbestos inside; *d*, a small plug of asbestos; between *c* and *d* a mixture of dry sodium carbonate and charcoal; *e*, a fire-clay chimney $1\frac{1}{2}$ inches in diameter, with a thin bridge of fire-clay to support the tube between *c* and *d*; *h*, a strip of muslin $\frac{1}{8}$ inch wide wrapped around the tube and tied.

much frothing a small quantity of alcohol may be introduced by the funnel-tube.

(a) *Marsh's Original Method.*—To prove the presence of arsenic in the gas Marsh proposed to condense the free metal on cold porcelain held in the flame (Fig. 34, c). It is like a spot of soot, black, or seal brown. Many spots can be obtained upon evaporating dishes or crucible lids, and tested later by different reagents to distinguish them from the antimony stains which they resemble closely.

(b) *Berzelius' Modification.*—The most delicate, reliable, and, indeed, necessary method for detecting the arsenic with the Marsh apparatus for forensic purposes is to heat the gas while passing through the long

¹ Chittenden and Donaldson, Amer. Chem. Jour., 1880–81, ii, 236; Fresenius, Qualitative Analysis, American edition, New York, 1915, p. 284 and 578.

exit-tube by applying to it one or more burners with chimneys to confine the heat. For the best results the tube may be constricted at points just beyond the part heated, and the constricted part kept cold by a wet muslin strip (Fig. 35, *h*).

If the heat is maintained for an hour all the arsenic will be separated from the mixture and collected as a mirror-like ring inside the tube between *k* and the strip of wet muslin. The discrimination tests given below can be used to confirm the arsenical nature of this metallic ring as well as for the spots on porcelain. If the suspected compound be in the *arsenic* form the reaction is much more slow in appearing than when the substance is in the *arsenous* form. Before reaching a negative conclusion considerable time must be given to this reaction.

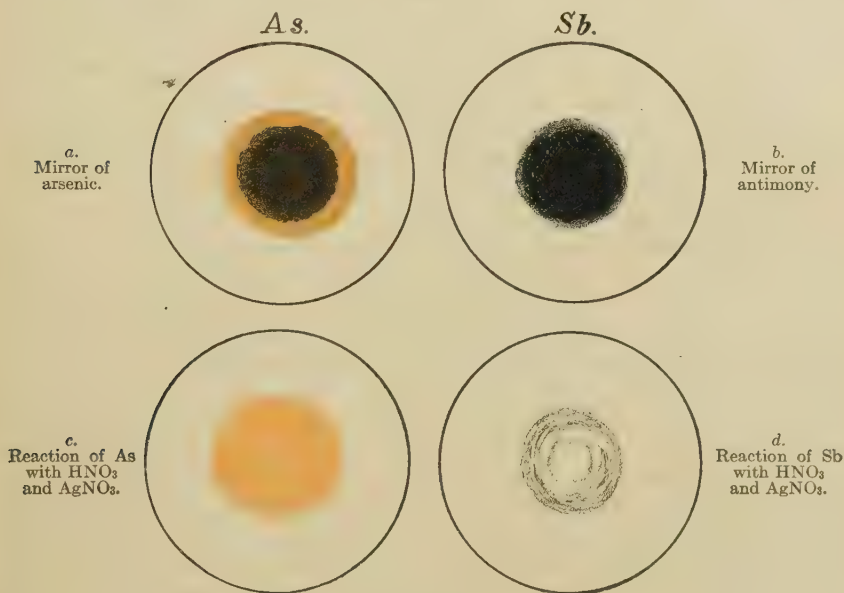


FIG. 36.

Fallacies.—Antimony is deposited under the same conditions as arsenic and in a form closely resembling it, whether in the spots on porcelain or the mirror-like ring in the heated tube, but the arsenic mirror is at a little distance beyond the flame and brownish shading to black (Fig. 36, *a*), while the antimony is close to the flame, sometimes on both sides of it, and tin-like in luster.

The arsenic stains are soluble in warm solution of *calx chlorata* or in *liquor sodæ chloratæ*, while the antimony is insoluble, or only very slowly and sparingly soluble. Dissolved by heating gently with a few drops of a solution of ammonium molybdate in nitric acid the arsenic gives a yellow precipitate, whereas antimony forms none. Another deposit dissolved in nitric acid and dried by cautiously heating leaves a

whitish spot which, if arsenical, turns red when touched by a drop of strong solution of silver nitrate (Fig. 36, *c*); if antimonial, there is no change of color (Fig. 36, *d*). Another deposit, if arsenical, dissolves in ammonium sulphid and on evaporation leaves a yellow stain soluble in ammonia, but insoluble in hydrochloric acid. The residue of antimony sulphid would be orange red, insoluble in ammonia, but soluble in strong hydrochloric acid.

The extraordinary sensitiveness of most of the tests for arsenic requires that the analyst should be very careful that the apparatus is clean and the chemicals are of ascertained purity. In medicolegal analysis it is well to carry on simultaneously a parallel blank examination, similar in every respect but that of containing the suspected matters. Traces of arsenic have been found in zinc, copper, sulphuric acid, hydrochloric acid, even in filter-paper, and in common illuminating gas. Glass vessels that have been cleaned with shot may have enough left on them to lead to a false conclusion.

Interferences.—The perfection of Marsh's test is impaired if chlorids, hydrochloric acid, nitrous compounds, or nitric acid is present. If salts of silver or mercury are present, they may decompose the arsenic terhydrid in the flask as soon as it is generated.

Delicacy.—According to Wormley,¹ to operate this test even on a small scale requires at least 100 grains of the liquid. The least amount that would yield a satisfactory spot on porcelain is about $\frac{1}{50000}$ grain of arsenic trioxid. When the gas is not ignited but heated in the exit-tube so as to get all the free metal at one point, we get a degree of sensitiveness beyond that reached by any other test known to chemistry. By this Berzelius' modification of Marsh's test a characteristic deposit on the glass can be obtained from $\frac{1}{50000}$ grain dissolved in 100 grains of liquid.

5. Fleitmann's Test.—When zinc or aluminum is heated with excess of potassium hydroxid or sodium hydroxid in a mixture containing arsenic trioxid or trisulphid the gas arsenic terhydrid is evolved. The apparatus required is a generating flask with a delivery tube dipping into a 4-per-cent. solution of silver nitrate. It is sometimes more convenient to use a test-tube covered with filter-paper wet with silver nitrate, as in Gutzeit's test (Fig. 32). The suspected liquid, made strongly alkaline with pure sodium or potassium hydroxid, is put in the flask or the test-tube with a few pieces of sheet aluminum or pure zinc and gently heated. The arsenic terhydrid reduces the silver as a black precipitate, leaving arsenic trioxid and nitric acid in solution. If the test-tube is used a black spot appears on the paper cover. By means of this test we can detect arsenic in the presence of antimony, as antimony terhydrid is not evolved by it. It will not detect arsenic as arsenic acid, and as it forms solid hydrid in the flask, holding back one-fifth of the arsenic present,² it is not available for quantitative purposes. It is liable to a fallacy from the fact that free hydrogen after some time

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 285.

² Clark, *Jour. Chem. Soc.*, 1893, lxiii, 884.

and phosphin both reduce the silver nitrate, hence the presence of arsenic trioxid in the silver solution must be proved (see p. 232).

6. **Gosio's "Arsenic Fungus" Test.**¹—The intense garlicky odor, probably due to di-ethyl-arsin, a volatile product evolved by a common mold, *Penicillium brevicaulis*, growing on arsenical substances (p. 245) is the basis of a qualitative test that is applicable directly to suspected material of complex composition. With a few biologic procedures $\frac{1}{100000}$ gram of arsenic can be detected in contaminated flour by the characteristic odor referred to. First, a pure culture of the mold should be made as follows: Into a test-tube is placed moist cotton wool carrying disks of raw potato. Plugged with cotton wool the tube is sterilized by twenty minutes heating in an autoclave at 115° C. With a platinum loop and suitable precautions the disks are sown with the spores of penicillium brevicaulis, and cultivated for a week or two at 30° C. until it has grown to a white fluffy mass. This can be kept as a stock culture for a long time.

Test.—Having mixed in a test-tube about 5 grams of the suspected substance with 10 grams of rasped raw potato and a little water and closed the tube with cotton wool, the mixture is sterilized, cooled, and spores of the pure mold culture added. This tube and two control tubes, one with and the other without arsenic are kept twelve to seventy-two hours at 32° C. If arsenic be present in a tube the peculiar odor develops. Tellurium compounds also evolve a volatile substance under the same conditions having the garlic odor. But tellurium is a very rare element and not at all likely to appear in the material suspected of arsenic. The same can be said of selenium compounds, which under the conditions of Gosio's test yield a volatile substance with a more offensive odor like that of mercaptan.² But gases of a garlic odor are not produced from sulphur, phosphorus, antimony, boron, and bismuth. The test is prevented by mineral acids, which may be neutralized with calcium carbonate and by alkalis which can be neutralized with tartaric or citric acid. If one has the proper mold culture the procedure is simple as it does not involve the destruction of organic matter. The test is more delicate than Bettendorff's and is equal to Marsh's. For a week the odor can be demonstrated when the material contains only 0.0001 gram of arsenic.³

Estimation in Urine, Gastric Contents, and Viscera.—The vomited matters should be spread in a thin layer on a large dish and carefully searched for grains of white arsenic, Paris green, or yellow sulphid. For casual or preliminary examination the suspected material may be treated as suggested above by Reinsch's test. The presence of the smallest amount revealed by this test is significant, as arsenic is not a normal constituent of the body nor should it be present in the food. If any compound of arsenic should be found free in the gastric contents,

¹ Arch. ital de Biol., 1892, xviii, 253. Berichte, Berlin, 1896, xxix, 2728; 1897, xxx, 4024.

² Maasen, Arb. a. d. Kaiserl. Gesdhtsamt, 1902, 478.

³ Abel and Battenberg, Zeitschr. f. Hyg., 1899, 32, 440.

or if it should be obtained by testing, a specimen of it must be carefully marked and set aside to show in court.

When it is desired to make a *quantitative* estimate it is necessary to destroy the organic matter. This may be done by mincing the tissue into fine shreds, bruising these in a mortar, heating over a water-bath in pure dilute hydrochloric acid¹ (best made in the laboratory), and adding from time to time small portions of potassium chlorate until the solids are completely dissolved in a clear yellow fluid and continuing a gentle heat until the odor of chlorin disappears.² This fluid is treated with solution of sulphur dioxid to reduce the arsenical compound to the arsenous form, then concentrated on a water-bath and filtered. Reedy³ has shown that the addition of a small amount of a soluble iodid to the solution facilitates the precipitation of the arsenous sulphid from solutions of the arsenates. A slow stream of pure hydrogen sulphid passed through the filtrate will precipitate the arsenic as arsenous sulphid with other matter. The precipitate is collected on a filter, thoroughly washed, and treated with ammonia water, which dissolves out the arsenous sulphid, leaving various impurities behind. The filtered solution is evaporated to dryness in a porcelain dish, the residue warmed with strong nitric acid until completely oxidized, and solution of sodium hydroxid added in slight excess. The mixture is evaporated to dryness, the residue moistened with pure sulphuric acid, and heated cautiously on a sand-bath until fumes cease to escape. The carbonaceous product is boiled out with acidulated water and the solution filtered. The filtrate should be colorless and, if the process has been properly executed, contains all the arsenic free from organic matter. As the arsenic generally exists in the solution wholly or in part as arsenic acid, sulphurous acid should be added to reduce it to the arsenous condition, and the mixture gently heated until all excess of the sulphur dioxid has been expelled. A definite part of this solution may be reserved for determining the amount of arsenic by precipitation with hydrogen sulphid, as described below, while the remainder may be subjected to Reinsch's, Marsh's, and other tests to establish fully its arsenical character.

The above method is objected to on account of the liability to lose a small amount of arsenic carried off as vapor by the chlorin. This objection cannot be made to the following method (*Taylor's*⁴), which is designed to convert all the arsenic into a volatile chlorid and to separate the vapor from organic matter by distillation. The organic material should be cut into fine shreds, well dried in a water-oven, and pulverized in a mortar. The powder stirred in strong, pure hydrochloric acid should then be set aside for twenty-four hours. Having adjusted a flask to the inner tube of a Liebig's condenser connected with a receiver, the acid mixture is poured into the flask and heated over a sand-bath almost to dryness. It is treated a second time with hydrochloric acid

¹ Fresenius, *Qualitative Analysis*, American edition, New York, 1915, p. 585.

² Consult also p. 46 in *Section on General Principles of Toxicology*.

³ *Jour. Am. Chem. Soc.*, 1921, 43, 2419.

⁴ Taylor, A. S., *On Poisons*, 1875, p. 319.

and again distilled. Both distillates, representing all the arsenic, should be collected in a receiver containing distilled water. For determining small quantities of arsenic the most delicate method is that employed by Chittenden and Donaldson¹ and by Sanger.²

A method devised by Strzyzowski is based upon the property of magnesium oxid to hold arsenic as a pyroarsenate in the ash after calcination. Thus the organic matter may be destroyed without loss of arsenic by volatilization, as the pyroarsenate is highly resistant to heat. Furthermore, the danger is avoided of admitting the arsenic which may contaminate hydrogen sulphid when that is used. The procedure employed at the Paris Laboratory of Toxicology,³ minces 100 grams of the suspected substance and places the pulpy mass in 35 mils. (c.c.) of a solution of arsenic-free crystals of magnesium nitrate with addition of a little calcined magnesium oxid to prevent acidity which would favor the loss of arsenic. The mixture is heated in an oven to about 250° C. and allowed to stand for three hours. Thus heated and dried, arsenic in the organic mixture unites with the magnesium to form a pyro-arsenate. A porcelain capsule containing the spongy mixture is heated in a furnace at a dull red glow and incineration is complete in twenty minutes. The cold white ash is extracted by 10 mils. (c.c.) of water and 5.5 mils. (c.c.) of 50 per cent. pure sulphuric acid, the liquid filtered and the filtrate made up to 20 mils. (c.c.) by washing the residue on the filter with dilute sulphuric acid. From this solution all the arsenic is recovered by the Marsh test. When arsenic is present in toxic amounts a more *rapid process* of calcining is possible. Allowance must be made for a small and insignificant loss by volatilization. This process places the minced pulp in the solution of magnesium nitrate with a pinch of magnesium oxid, evaporates it rapidly by heat and calcines it directly at a higher temperature after the addition of pure nitric acid. By this procedure the white ash is obtained in a few minutes.

In order to *estimate* the arsenic, the total quantity of fluid obtained as above from any organ, such as the liver, should be divided into equal parts and one or more of these parts used to get a deposit of metallic arsenic in the heated tube by the Marsh-Berzelius method. The section of coated tube is cut off and weighed, and then washed free from arsenic with nitric acid or solution of sodium hypochlorite and weighed again. The difference represents the amount of arsenic in the portion of the material used. According to Rettgers,⁴ the brown deposits which are more or less transparent consist of the suboxid, As_2O , and hydrid, AsH , hence these quantitative results can never be absolutely accurate. Another method of *estimating* is by converting the arsenic into sulphid. A measured fraction of the dissolved materials acidified with hydrochloric acid is treated with a stream of pure washed hydrogen sulphid

¹ Chittenden and Donaldson, Amer. Chem. Jour., 1880-81, ii, 236.

² Sanger, Proc. Amer. Acad. Arts and Sci., 1891, xxvi, 24; also Fresenius, Quantitative Analysis, American edition, New York, 1886.

³ E. Kohn-Abrest, La science et la vie, Paris, December, 1920; January, 1921.

⁴ Blyth, A. W., Poisons, Effects and Detection, 4th ed., 1906, p. 583.

gas. The yellow precipitate is collected on a filter, thoroughly washed,¹ and then dissolved in ammonium hydroxid. By evaporating the solution thus obtained on a water-bath, the ammonia is removed and the dried sulphid, after treatment with carbon disulphid to dissolve out any free sulphur that may be present, is weighed, and the calculation made on the basis that 100 parts of the sulphid contain 60.98 of elementary arsenic. As arsenic acid and the arsenates are precipitated very slowly by hydrogen sulphid they will require other treatment (see p. 230).

The reaction between *silver nitrate* and arseniuretted hydrogen is the basis of another method for stating the amount of arsenic. Having started the process of hydrogen formation in the Marsh apparatus a gas-burner should be applied to the delivery tube to test the materials. If no stain appears on the glass tube after heating ten minutes the apparatus may be considered arsenic-free. The end of the tube should be extended and bent down at a right angle so as to dip into a weak solution of silver nitrate. The suspected material is now poured into the flask and the gas allowed to pass through the silver nitrate solution. The end of the process will be known by dipping the tube into a fresh sample of silver nitrate; it should not darken it. In this process the nitrate is decomposed, the free silver deposited as a black precipitate, and the arsenic trioxid will be left in solution. Any excess of silver nitrate can be removed by hydrochloric acid and filtration; then the arsenic in a fractional portion may be precipitated by hydrogen sulphid and the precipitate dried, washed with carbon disulphid, again dried, and weighed. When the arsenic trioxid is present in small quantity, the hydrogen sulphid will not make a precipitate at once, but cause a yellow color, deep in proportion to the arsenic present. A fractional portion of the tested silver solution freed from silver may be put in a Nessler cylindric glass, and a known quantity of saturated hydrogen sulphid solution added. In another cylinder the same quantity of hydrogen sulphid solution should be put, and a weak hydrochloric acid solution of arsenic trioxid of known strength added to it from a buret until the same color is produced. The amount can then be calculated from the reading of the buret.

Estimation by Gutzeit Method.—In applying the Gutzeit test for quantitative analysis, Sanger and Black² proposed the following modification: By a hydrogen generator, as in a Marsh test, arsin is evolved from the prepared suspected solution, but in this method quantity is determined by the extent of the reaction of arsin with concentrated mercuric chlorid. This reaction yields a compound which deepens in extent and color from lemon yellow through orange red to brown, according to the richness of the product in arsenic. These colors are

¹ Another method of disposing of the impurities is that of Fresenius (Qualitative Analysis, American edition, 1915, p. 589). The sulphid on the filter is decomposed with strong nitric acid and then heated for a time with strong sulphuric acid until the mass becomes pulverulent; then the arsenic is taken up with dilute hydrochloric acid, filtered and reprecipitated with hydrogen sulphid. The dried sulphid is rid of free sulphur by treating with carbon disulphid and then weighed.

² Proc. Am. Acad. Arts and Sci., 1907, 43, 297, 324.

shown best on strips of white paper sensitized with mercuric chlorid,¹ as is represented in the colored plate (Plate 4), which gives amounts that produced them in 1000 mg. of arsenic trioxid. They develop darker tints (Plate 4) when immersed in hydrochloric acid (1 : 1) for two minutes at not over 60 degrees. A few minutes treatment with ammonium hydroxid (Plate 4) gives them a black color. The colored bands in the Plate 4 are based on *comparison standards*, made by dissolving 1 gram of powdered and desiccated arsenic trioxid in a small quantity of arsenic-free sodium hydroxid, neutralizing with arsenic-free sulphuric acid and sufficient boiled water added to make a liter at 25° C. of this mother solution (I), 10 mils. (c.c.) are diluted with freshly boiled water to make a liter of solution (II) representing 0.01 mg. of arsenic trioxid in each 1 mil. (c.c.). Definite volumes of solution (II) are added to the hydrogen generator, which is cleaned and freshly charged for making each standard band. A series of colored paper bands are thus prepared for comparison, which are the originals of the more or less accurate reproductions in Plate 4. Fading of color is inevitable, but may be retarded by sealing the bands in dry glass tubes containing a pinch of phosphorus pentoxid beneath a layer of dry absorbent cotton and keeping them in dark containers. Strips of heavy white filter-paper 4 mm. wide are sensitized for the comparison test by soaking in 5 per cent. solution of recrystallized mercuric chlorid. After drying they are cut into lengths of 7 cm. and kept dry in a dark, tightly-stoppered bottle at the bottom of which is calcium chlorid covered with absorbent cotton.

The *apparatus* is best constructed all of glass with ground joints, as in Fig. 37. However, it may be put together of ordinary laboratory appliances.² A bottle holding 30 to 50 mils. (c.c.) has a rubber stopper with two perforations, one for a thistle tube narrowed to 2 mm. at the end which extends nearly to the bottom of the bottle. The exit for the gas is by a vertical "drying" tube, which widens above to about 15 mm. The wide upper end of this drying tube has inserted through a perforated cork a narrower tube of 4 mm. caliber, which bends at a right angle extending 9 cm. horizontally.

The *procedure* is to put 3 grams of arsenic-free granulated zinc in the bottle and a strip of the sensitized mercuric chlorid paper in the

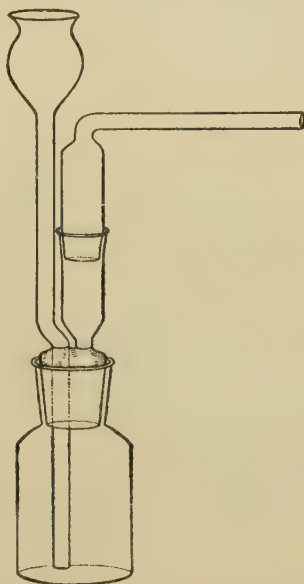


FIG. 37.—Apparatus for the quantitative Gutzeit method. (From Autenrieth's "Detection of Poisons.")

¹ Cribier, Jour. Pharm. Chim., 1921, 24, 241.

² U. S. Pharmacopeia, 9th rev. ed., p. 584.

4 mm. open tube. The "drying" chamber of the gas-exit tube is loosely plugged with clean absorbent cotton or glass wool that has been dried over sulphuric acid. Beneath the cotton as a precaution against possible interference by hydrogen sulphid is a moist disk of filter-paper once wet with lead acetate solution and dried, or a plug of moist lead acetate glass wool. The operation begins by adding 15 mls. (c.c.) of pure dilute hydrochloric acid (1 : 6), and running the hydrogen ten minutes as a blank test for purity of the reagents. If they are arsenic-free the strip is not stained. An aliquot part is now added of the suspected solution, which should be as free as possible from interfering organic matter and sulphur compounds that in the presence of sulphuric acid might liberate hydrogen sulphid. If arsenic be present a yellow tint appears on the test-paper in a few minutes, and deepens for thirty to forty-five minutes. Antimony has no color effect on the test paper short of 0.070 mg., above which amount the paper turns gray. Immersing the antimony strip in ammonium hydroxid five minutes develops slowly a black band.

Delicacy.—In practice a characteristic yellow tint can be obtained from 0.001 mg. of arsenic trioxid or a black band from 0.003 mg. of antimony trioxid when developed with ammonium hydroxid. The method is said to be accurate within 10 per cent. If antimony is to be estimated,¹ bands of mercuric chlorid test-paper can be standardized for comparison by the reaction of a solution made by dissolving in a liter of water 2.306 grams of recrystallized tartar emetic. This mother solution (I) represents 1.0 mg. of antimony trioxid for each 1 ml. (c.c.). By diluting 10 mls. (c.c.) of solution (I) to make a liter, solution (II) is prepared, which contains 0.01 mg. of antimony trioxid for 1 ml. (c.c.). This is used to generate known amounts of stibin which acting on the test-paper fixes the standard.

Mai and Hurt's Electrolytic Estimation.—By using electrolysis for generating arsin this method avoids the possibility of error from impure zinc. It is claimed² that any arsenical electrolyte yields arsin quantitatively at the cathode without previous destruction of the organic matter. Of simple organic liquids like beer and syrups this may be true, but not of the urine which gives results in excess unless the arsenic is separated from organic union. The amount of organic matter being small in the urine a direct and rapid method of destruction is available. Concentrated sulphuric acid containing one-thirtieth its volume of nitric acid is added to the solid urine which has been previously evaporated in a capsule to dryness on a water-bath. The mixture is heated gently until the dense white acid fumes are all given off. The charred residue is extracted with boiling water, filtered, and the filtrate introduced at once into the testing apparatus.

The *apparatus* is shown in Fig. 38 which is about one-fourth its natural size. *A* is the U-shaped reduction cell with electrodes *a* and *e* of pure lead about 1 to 2 mm. thick. *B* is a modified Mayerhofer

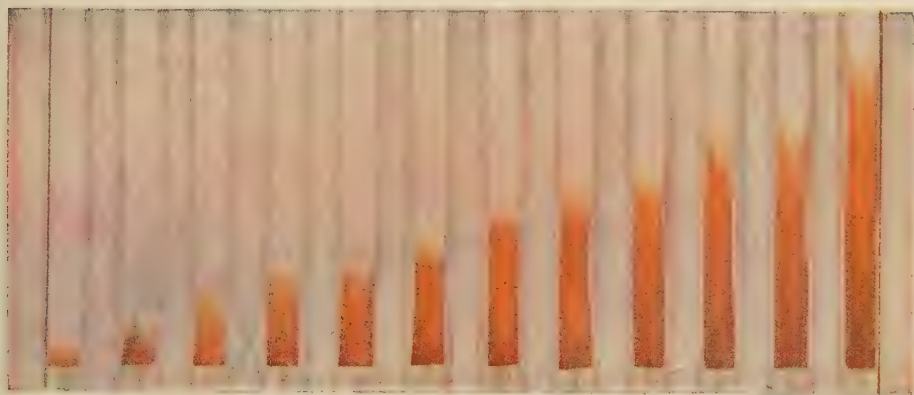
¹ Sanger and Riegel, Proc. Amer. Acad. Arts and Sci., 1909, 45, 21–27.

² Thorpe, Proc. Chem. Soc., 1903, 19, 183.

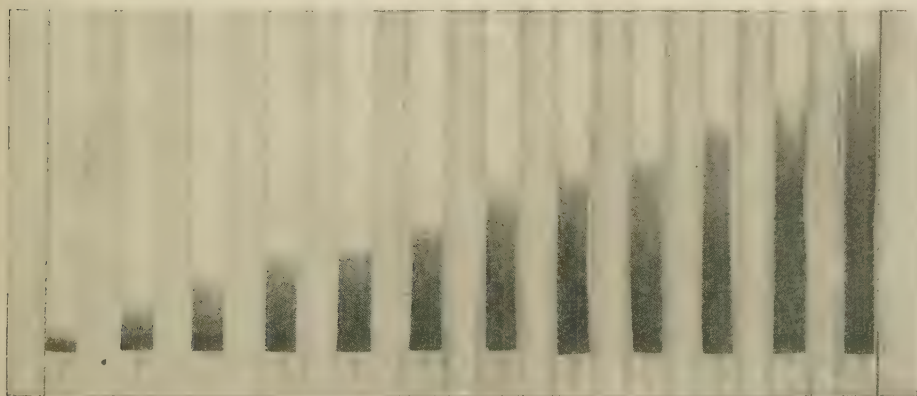
PLATE 4.



2 5 10 15 20 25 30 35 40 50 60 70
Standard Arsenic Bands in Micromilligrams of As_2O_3 (Initial).



2 5 10 15 20 25 30 35 40 50 60 70
Standard Arsenic Bands in Micromilligrams of As_2O_3 (Hydrochloric Acid Development).



2 5 10 15 20 25 30 35 40 50 60 70
Standard Arsenic Bands in Micromilligrams of As_2O_3 (Ammonia Development).

[From Autenrieth's "Detection of Poisons."]

absorption tube with 5 bulbs containing 0.01 N-silver nitrate solution. The connection is by a tube *g* filled with pieces of pumice saturated with basic lead acetate solution to arrest traces of hydrogen sulphid. Each electrode is one piece of lead C.P. shaped above to a rod 5 mm. thick which without being soldered in the cell is cemented into the glass tubes *b* and tightly fit the stoppers. The safety tube *c* has a little water at the bend that permits the escape of the oxygen freed in the anode chamber. The capacity of the funnel *d* is about 25 mls. (c.c.). Its constricted end dips into the electrolyte to about 2 cm. below the surface.

Procedure.—The cell *A* is filled to the extent shown in Fig. 38 with 12 per cent. arsenic-free sulphuric acid and a few drops of pure zinc sulphate solution. The bulbs *B* are filled with 10 mls. (c.c.) of

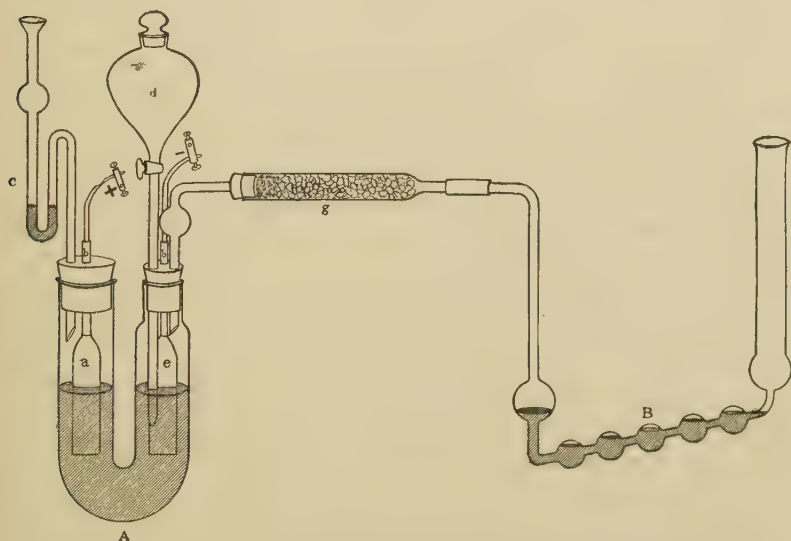


FIG. 38.—Apparatus for the electrolytic estimation of arsenic. (From Autenreith's "Detection of Poisons.")

0.01 N-silver nitrate solution. Purity of the reagents is tested by passing for one hour a 110 volt direct lighting electric current regulated by rheostat to 6 to 8 volts, and 2 to 3 amperes. If the silver nitrate in the bulbs be unchanged the apparatus and contents are fit for the test. The suspected liquid 10 mls. (c.c.) is introduced in *d* and dropped as slowly as possible, the last traces in the funnel being washed in with a little water. In two or three hours all the arsenous and arsenic acids will have been changed to arsin at the cathode and the silver nitrate solution reduced proportionately to finely divided silver. The reaction is as follows: $\text{AsH}_3 + 6\text{AgNO}_3 + 3\text{H}_2\text{O} = \text{H}_3\text{AsO}_3 + 6\text{HNO}_3 + 6\text{Ag}$. At the end of the operation the silver nitrate in the bulbs is poured through a small asbestos filter, the bulbs and filter washed in with 3 to 4 mls. (c.c.) of water, and the filtrate tested for surplus of the

0.01 N-silver nitrate with 0.01 N-potassium sulphocyanate according to Volhard's method of titration, using ferric alum as an indicator. The difference between the finding and the original content of the test fluid gives the silver nitrate reduced. Each 1 mil. (c.c.) of the silver nitrate 0.01 N-solution reduced represents 0.125 mg. arsenum in the suspected liquid.

Delicacy.—The least amount detectable by this method is 0.02 mg. of arsenum.

Detection in Wall-paper.—When there is reason to think that the amount of arsenic is considerable resort may be had to Reinsch's test. Five square inches of the paper cut finely are put in a dish with dilute hydrochloric acid and heated on a water-bath for fifteen minutes. The solution is then decanted into a test-tube, a piece of polished copper-foil added, and then boiled for ten minutes. The arsenical coating on the copper can be verified by the confirmatory tests given above (p. 224).

When the amount present is so small as to give a doubtful result to Reinsch's test it may still be revealed by the Marsh-Berzelius method. The arsenic is dissolved from the paper, as stated above, and the acid solution poured into the Marsh apparatus (Fig. 35). The blackness of the arsenical mirror formed in the glass tube when compared with a series of standard arsenical mirrors will give an approximation to the quantity. Chittenden¹ has worked out a very delicate method for detection of minute quantities.

Distribution of Absorbed Arsenic.—Besides that which may be found in the contents of the stomach and intestines, a variable proportion of arsenic is absorbed, and by the blood and other fluids is distributed to different organs and tissues. This latter part has certainly had a poisonous effect, whatever may be said of that found unabsorbed. Even when none has been found in the contents or even in the structure of the stomach and the intestines, the liver, kidneys, spleen, and heart have rendered up their store to the analyst. The muscular and bony tissues and the brain are also places for the deposit of absorbed arsenic. The experiments of Dutcher and Steel² showed that after administration of a single dose of 35 mg. of arsenic to animals, the metal preponderated in the muscles, liver, and intestinal wall respectively. Early after the dose the blood held fourth and the skin fifth place in the retention. After twenty-one days these tissues had lost all detectable arsenic; a single non-poisonous dose of arsenic was eliminated in about fifteen days.

It not infrequently happens that the arsenic is taken in a very soluble form, and, the patient surviving for two weeks or even less, no poison can be detected in the viscera usually examined. This is due to the activity of the circulation in the soft tissues and the readiness with which the poison is eliminated. Under such circumstances several observers have discovered the poison still present in the cancellated structure of the bones and in the nails and hair. In a case reported by

¹ Fresenius, *Qualitative Analysis*, American edition, New York, 1915, p. 575.

² *Jour. Am. Chem. Soc.*, 1914, 36, 770.

Wood,¹ he detected by Sanger's method arsenic in the urine ninety-three days after a single large dose had been administered, causing acute symptoms and having a sequel of paralysis. Stich² reported a case in which arsenic was found in the gastric contents of a woman who had been poisoned by the introduction of a large amount in the vagina. He reported another case of poisoning *per vaginam* in which arsenic was found in the gastric contents and feces of a woman, and some was obtained from the organs of her three months' fetus.

The case of Jennie Cramer is very important in medicolegal annals, showing that in order to make an estimate of the amount present in the body, it is necessary to analyze not only the internal organs, but specimens of the muscles, bones, nails, and hair must be included. The post-mortem revealed no evidence of inflammation of the stomach. Still the prosecution held that though the body was found in the water, as arsenic was discovered in the brain and other tissues, death probably occurred not from drowning, but from the sudden cerebral impression produced by the poison having been taken in a very diffusible state. A few days after death the analysis was made and the following instructive illustration of distribution was obtained, as stated by Chittenden³:

The calculation is in grains of arsenic trioxid, As_2O_3 : Stomach and esophagus, 0.158; liver, 0.218; intestines, 0.314; kidneys, 0.029; heart, 0.112; lungs and spleen, 0.1528; brain, 0.765; trachea, larynx, and tongue, 0.081; diaphragm, 0.010. The internal organs yielded a total of 1.1694 grains. From different parts of the body the muscular and bony structures, with a total weight of 24 pounds, $14\frac{1}{2}$ ounces, were subjected to the same analysis, with the result of finding 0.852 grain of arsenic. With these data it was calculated that the entire body, including the viscera, contained a total of 3.1192 grains. While it strengthens a case to prove that the corpse contains a fatal quantity, it is not essential for conviction, as shown in the trial of Mrs. Maybrick, when only $\frac{1}{3}$ grain was found in the viscera analyzed.

McNally⁴ gave the details of the retention of arsenic which showed that in cases where death is delayed the distribution is more nearly equal than when the duration is short.

Case 1 died four and a half hours after taking an unknown quantity of arsenic and in which the stomach was not emptied. The autopsy and analysis were made nine days after death. For 100 grams of tissue the stomach walls contained grams of *arsenum*, 0.0249; large intestine, 0.0262; liver, 0.0144; stomach contents, 0.8926; small intestine, 0.0134; kidneys, 0.0175; heart, 0.0065; pancreas, 0.0095; lung, 0.0021; gall-bladder, 0.0042; brain, 0.0002.

Case 2, male, sixteen years old, died after three weeks from first dose, and ten days from second dose. The early symptoms were of

¹ Boston Med. and Surg. Jour., 1893, cxxviii, 414.

² Münch. med. Wochenschr., March 12, 1901, xlviii, 425.

³ Amer. Chem. Jour., 1883-84, v, 8.

⁴ Jour. Amer. Chem. Soc., 1917, xxxix, 826.

gastro-enteric disturbance; later, numbness and tenderness in the extremities led up to feeble muscles, complete paralysis, and death. The analysis was made eighteen hours after death. For 100 grams of tissue, the spinal cord contained grams of *arsenum*, 0.0011; blood, 0.0005; stomach walls, 0.0005; stomach contents, 0.0005; kidneys, 0.0016; spleen, 0.0013; liver, 0.0013; urine, 0.0017.

Failure to Detect.—Instances are known of undoubted poisoning in which no trace of the arsenic has been found in the parts usually examined. The eliminating organs had time before death to expel the unnatural substance.

"Normal" Arsenic?—Gautier¹ found arsenic in the tissues of the thyroid and thymus glands, the skin, and the brain, chiefly in the form of nuclein iodid. Later² he reported it constantly present in the fresh thyroid of man. A trace was found in the hair of a man and also of a woman, neither of whom had ever taken arsenic. Some was detected in the thymus of a lamb. Traces were discovered in the mammæ of a cow and in 2 quarts of her milk. Fresh bone furnished a trace. The brains of two still-born children showed its presence, but it was absent in a third. He failed to find arsenic in the presumably healthy tissue of liver, kidney, spleen, muscles, testicles, pituitary gland, mucous membrane, cellular tissue, lymphatics, salivary glands, suprarenal capsules, bone-marrow, uterus, ovaries, blood, urine, and feces. Upon examining various foods he found it absent from bread, fish, eggs, and meats, excepting the tissues named above, viz., milk, thymus, thyroid, skin, and brain. It was present in the following vegetables: cereals, turnips, cabbages, and potatoes.

Knecht and Dearden³ reported that they found measurable quantities of arsenic in 1 gram of the hair of several persons having arsenical neuritis, and a trace in the same amount of hair from healthy subjects. Having found arsenic in the urine of well persons living in Manchester, Thomson⁴ extended his research, with the result of finding it in the urine of workers in impure metals and those dwelling nearby who breathed the smoky air. He found minute traces in the thyroid, lungs, and hair, but none in heart, spleen, liver, and kidney.

Hödlmoser⁵ reached a conclusion opposed to that of Gautier. His research showed that arsenic is not a normal constituent of the human body. He did not find a trace of arsenic in the liver and pancreas in 18 cases examined by Gautier's method, nor in 15 other cases in which the same viscera were examined by another process esteemed more delicate. In repeating the experiments of Gautier referred to on different tissues he always obtained negative results. Kunkel,⁶ with

¹ Bull. de l'Acad. de Méd., 1899, 3 S., xlii, 561.

² Ibid., 1900, 3 S., xliii, 116; Ibid., xlv, 190; also Compt. rend. Acad. d. sc., 1899, cxxix, 189 and 929; 1900, cxxx, 284; 1900, cxxxi, 361; 1902, cxxxiv, 1394; 1902, cxxxv, 812; 1903, cxxxvii, 295; see also article by Bertrand, Annales de l'Institut Pasteur, 1902, xvi, 553; 1903, xvii, 1.

³ Lancet, 1901, i, 854.

⁴ Jour. Amer. Med. Assoc., 1904, xliii, 180.

⁵ Zeitschr. f. physiolog. Chem., 1901, xxxiii, 329.

⁶ Ibid., 1905, xlv, 527.

very delicate tests, failed to get arsenic traces with certainty in any organ taken from a normal animal.

Twenty years after his first announcement Gautier¹ rectified the results published in 1899 and 1903 with reference to the quantity of arsenic in "normal" tissues (0.75 mg. in 100 gm. of thyroid), which he later thought excessive, and the error was probably due to traces of hydrogen arsenid in the hydrogen sulphid used. He did not modify his former conclusions as to its presence, its location, especially in skin, hair, and beard, and mode of elimination, but suggested extreme care in estimating the minute amounts of arsenic, to have all reagents free of it.

The analysts following Gautier's first publications who found arsenic in human organs gave the proportions much smaller than his figures, and traces were detected in some organs he pronounced non-arsenical. On the one hand, the names of those agreeing with Gautier are Bertrand,² Schaeffer,³ Pagel.⁴ Among those who do not agree to call arsenic "normal" to human tissues are Cerny,⁵ Ziemke,⁶ Wieser,⁷ Bloemendal,⁸ Warren.⁹ Analyzing many times human and animal tissue they found arsenic absent, or if occasionally present, in traces only. They infer that this inconstant trace does not justify the assumption that arsenic is normal to man.

It is likely that the minute amounts found are accidents due to environment, occupation, or the soil of the locality. If it should in any case be accepted as normal, Kunkel¹⁰ doubts its significance for forensic chemistry. The quantities alleged to be normal are so small that those required in judicial trials to be satisfactory proof "must be regarded as an entirely different and much higher order of magnitude."

Arsenic Pentoxid (Chemical Formula, As_2O_5 ; Synonym, Arsenic Acid).—Arsenic pentoxid, As_2O_5 , commonly occurs in white, vitreous, deliquescent masses, but may be obtained as rhombic crystals. The pentoxid deliquesces in the air and changes to the true acid, $\text{As}_2\text{O}_5 + 3\text{H}_2\text{O} = 2\text{H}_3\text{AsO}_4$. This is a colorless, acid, syrupy liquid with a metallic taste. Like arsenic trioxid, it is an irritant poison. The free acid is not used in medicine, but some of its salts are. It is much used in the manufacture of dyes, although recently other oxidizers have supplanted it to a considerable degree. It responds to the same tests as arsenic trioxid, but has a peculiar reaction with silver nitrate, forming a brick-red precipitate (No. 4, Plate 3). It will respond to Marsh's test, but it is precipitated very slowly by hydrogen sulphid. If there

¹ Compt. rend. Acad. d. sc., 1920, 170, 261.

² Ann. d. l. Instit., Pasteur, 1903, 17, 1-10. Compt. rend. Acad. d. sc., 1902, 135, 809. Bull. d. l. Soc. chim. d. Paris, 1902, 27, 1233.

³ Annal. d. chim. Anal., 1907, xii, 52 and 97.

⁴ Dissertation, Univ. Nancy, 1900.

⁵ Zeitschr. f. Physiolog. Chem., 1902, 34, 408.

⁶ Vierteljsch. f. Gerichl. med., 1902, 23, 51.

⁷ Dissert., Univ. Würzburg, 1903.

⁸ Dissert., Univ. Leyden, 1908.

⁹ Autenrieth and Warren, Detection of Poisons, 5th ed., 1921, 174.

¹⁰ Ztschr. f. physiol. chem., 1905, xliv, 527.

is reason to think that either arsenic acid or any arsenate is present in the tested fluid it should be reduced to arsenous acid by a current of sulphur dioxid and the latter removed by passing carbon dioxid before the hydrogen sulphid is added to it. A solution of sodium arsenate, 4 pounds to the gallon, is in some states of the Union injected by undertakers through the nostrils into the stomach and into the thoracic cavity in order to arrest decay in warm weather. Sometimes cloths are wet with it and wrapped about the corpse to accomplish the same end.

Presence of Arsenic in Various Substances.—*Medicinal Preparations.*—The acidum arsenosum of U. S. Pharmacopeia (white arsenic, As_2O_3) is present to the amount of 1 per cent. in each of the following preparations: *Liquor acidi arsenosi*; *liquor potassii arsenitis* (Fowler's solution); *liquor sodii arsenitis* (Harle's solution). Donovan's solution, or *liquor arseni et hydrargyri iodidi*, contains 1 per cent. each of arsenous iodid, AsI_3 , and mercuric iodid, HgI_2 , while Pearson's, or *liquor sodii arsenatis*, contains 1 per cent. of exsiccated sodium arsenate. *Sodii arsenas* occurs as colorless, odorless prisms, soluble in water. *Sodii arsenas exsiccatus* is an amorphous white powder, permanent, and very soluble with slight decomposition. *Arseni iodidum* occurs as an orange-red crystalline powder, water soluble with slight decomposition.¹ The National Formulary adds two preparations—*liquor auri et arseni bromidi* containing 0.83 per cent. of AsBr_3 and 0.33 per cent. of AuBr_3 ; and *liquor potassii arsenatis et bromidi* (Clemen's solution), which corresponds to 1 per cent. of As_2O_3 . *Cacodylic acid* and its salts, *atoxyl*, *arsphenamin*, and other organic arsenicals are considered under a separate heading (p. 247).

In Commercial or Impure Drugs.—An arsenical paste has been applied to tumors by cancer quacks so unskilfully as to produce systemic poisoning by absorption. The manufacturers of gelatin-coated and sugar-coated pills sell large quantities of tonic pills containing arsenic as a constituent. It is often a contaminant of commercial glycerin and of subnitrate of bismuth. In 1 out of 8 samples of bismuth subnitrate examined Coad² found arsenic; it was present to the amount of 0.33 per cent. of the element. In this preparation it probably exists as bismuth arsenate, a form not readily absorbed because of its insolubility.³ An inquiry by the British Government⁴ revealed arsenic 0.0008 per cent. in a sample of tartaric acid made by a process using contaminated sulphuric acid from a Spanish source. Cameron⁵ reported the deaths of 10 cows from taking sodium sulphate impure to the extent of 0.1 per cent. of arsenic trioxid. Magnesium sulphate⁶ is sometimes contaminated with an arsenic compound so that a dose of 1 ounce would contain $\frac{1}{5}$ grain of arsenic. Traces have been discovered in samples of *liquor ferri chloridi* and in commercial sodium

¹ Brit. Med. Jour., 1900, ii, 823.

² Amer. Chem., New York, 1875, vi, 44.

³ Chittenden and Lambert, Amer. Chem. Jour., 1881-82, iii, 398.

⁴ Jour. Amer. Med. Assoc., 1907, xlviii, 2127.

⁵ Analyst, London, 1887, xii, 32.

⁶ Rattinger, Pharm. Jahresb., 1883-84, 515.

bicarbonate. Byrnes¹ reported a case of acute poisoning from arsenic in a can of baking powder. It is probable that the arsenic was added with criminal intent.

In Lead Projectiles.—Lewin² has found that the lead and antimony alloy of shrapnel bullets may contain 1 to 3 per cent. of arsenic. When one is embedded in the tissues, the alkaline juices release the arsenic to be harmlessly eliminated, but lead is retained and may cause plumbism.

In Coal Products.—Bayet and Slosse,³ and also Richet⁴ state that many serious industrial diseases are traceable to the arseniferous pyrites of coal and lignite. Symptoms analogous to chronic arsenical poisoning with arsenic in the hair and blood are known as "Pitch disease" of the pitch and briquet industry. It is also found in chimney sweeps, boiler cleaners, soot packers, gas, coke, and tar workers.

In Preservatives and Cleaners.—In order to keep wheat for planting it has been treated with an arsenical solution which does not alter its appearance or taste. Samples so treated have caused accidental poisoning. A mixture of white arsenic, tar, and soft soap is sometimes used as a "sheep dip" to destroy the parasites in wool. The sheep-washers have experienced poisonous effects from handling it and from drinking water from a vessel that once contained it. Taxidermists make use of an arsenical soap and an arsenical powder to preserve skins. The workmen have suffered, and it is stated that poisonous symptoms can be traced to the arsenic emanating from stuffed specimens kept in sleeping-rooms. Wholesale poisoning has followed the introduction, into a boiler, of a "cleaner" made from arsenic and sodium bicarbonate. A similar solution has been used as a "soft injection" or preservative of bodies for dissection. Dissectors handling the bodies are likely to have a local irritation about the finger-nails.

In Anilin Dyes.—Arsenic acid or arsenic pentoxid is frequently used as an oxidizer by the color-men in the preparation of anilin-red and other pigments. It is not a necessary ingredient of the pigment, and at this time is not so often found in it as formerly. The expense of washing out this residuum still sometimes deters the manufacturers, and the dye may come into the market with enough arsenic in it to give irritant properties to stockings, gloves, and cretonne bed-trimmings reddened with it. This impure anilin red has been used to color strawberry and raspberry syrups.

In Food and Drinking Water.—At Bell-Ville, Argentina, Alvarez⁵ observed cases of "Bell-Ville disease" which proved to be chronic arsenical poisoning due to contaminated drinking-water from a certain well. At the Paris Laboratory of Toxicology⁶ a study of the average foods in France showed that for 100 grams of the substance the content

¹ Jour. Amer. Med. Assoc., 1909, lii, 948.

² Münch. med. Woch., 1916, 63, 1649.

³ Bull. de l'Acad. roy. de Belgique, 1919, 29, p. 607; Compt. rend. Acad. de sc., 1919, 168, 704.

⁴ Compt. rend. Acad. de sc., France, 1919.

⁵ Revista Med. d. Rosario, 1919, 9, 5.

⁶ Kohn-Abrest, La Science et la Vie, Paris, December, 1920; January, 1921.

of arsenic stated in thousandths of a milligram was for bread, 0.69; fish, 12.9; eggs minus shell, 0.2; leafy vegetables, 0.2; potatoes, 1.12; milk, 0.4; wine, 0.5; common salt, 23.0; drinking-water, 0.5. These infinitesimal amounts are mostly due to the arsenicals sprayed as insecticides on food plants. Some of the poison must sink into the soil and water, and eventually be absorbed therefrom. The figures quoted are much too small to be toxic or to be classed with the amounts deemed significant in forensic medicine. Cazeneuve¹ reports cases of poisoning from arsenic sprays used in the vineyards. (See p. 246 for the important results obtained by Headden.)

In the Air.—Hydrogen arsenid² is the most deadly of all the inorganic compounds of arsenic. It has destroyed life in quantities so small as not to impart a garlic odor to the air. Reports have been classified³ in 84 cases of poisoning by inhaling hydrogen arsenid. In chemical experiments with it 10 were poisoned, 6 of them fatally. Impure hydrogen inhaled to show the squeaky voice has poisoned 5 with 2 deaths. Commercial acids, impure from arsenic yet used in industries to generate hydrogen, caused 38 cases with 15 deaths. Impure hydrogen used to inflate toy balloons produced 10 cases with 3 deaths. Large balloons have similarly been the source for 21 cases with 9 deaths. Traces of this poison have been found in common illuminating gas. By some writers this is the form supposed to be taken by the arsenic emanations of wall-paper, though other authorities suppose the emanation to be a volatile organic compound, such as di-ethylarsin. In the extraction of silver from certain ores, the cleaning of iron for tinning and of brass for bronzing, acids are used which liberate hydrogen. This nascent hydrogen unites with arsenical impurities in the metal, if any is present, and thus poisons the air breathed by the workmen. Six cases of arsenical poisoning have been reported⁴ caused by fumes from a coke stove and yet others due to the noxious smoke from arsenical ores treated in smelting works.⁵ N. W. Jones⁶ reported 5 cases, due to hydrogen arsenid fumes arising from refining of the zinc product in the gold cyanid process. He refers to 55 cases of poisoning from arsin collected from his bibliography. Koelsch⁷ adds 11 new cases to the 119 recorded of hydrogen arsenid poisoning. His cases occurred in the treatment by sulphuric acid to extract vanadium from ore containing 0.3 per cent. of arsenic. After three years without mishap the toxic gas was generated, inexplicably. An outbreak of hydrogen arsenid poisoning was observed in the crews of two submarine vessels.⁸ The symptoms were dyspnea, headache, vomiting, gripes, jaundice, albuminuria, and mild neuritis. Arsenic was found in the urine, hair, and finger-nails; it was detected in the

¹ Bull. de l'Acad. de Méd., Paris, 1921, lxxxv, 660.

² See Chapter on Gaseous Poisons, p. 347.

³ Witthaus, Toxicology, 1911, p. 389.

⁴ Taylor and Trubshaw, Brit. Med. Jour., 1911, ii, 1591.

⁵ D. E. Salmon, Am. Vet. Rev., 1911, 39, p. 14.

⁶ Jour. Amer. Med. Assoc., 1907, 48, 1099.

⁷ Zentralblatt f. Gewerbehyg., Berlin, 1920, 8, 121.

⁸ London letter, Jour. Amer. Med. Assoc., 1919, 73, 1148.

battery gases and the ultimate source traced to an alloy in the battery grids with an arsenic impurity unusually high.¹

In Beer.—In the health reports of France of 1878 it was said that the glucose used in brewing sometimes contained arsenic. It is left in the glucose by the sulphuric acid employed in the conversion from starch, when the acid is obtained from arsenical iron-pyrites. The Lancet (December 1, 1900) analyzes reports from many sources of extensive poisoning in Liverpool, Manchester, and the Midland counties of England attributed to arsenic in beer, and extending through six months. The most frequent characteristic symptoms were catarrh, puffiness of the eyelids, irregular pigmentation of the skin, herpes and other eruptions, local numbness, tingling, and pain, with final paralysis. Arsenic was detected in the urine and in the hair. The amount of arsenic found in different samples of beer varied from $\frac{1}{100}$ to $\frac{3}{100}$ grain to the gallon.

In the Household.—Many cases of poisoning, accidental or otherwise, have been traced to things in common domestic use. "Fly-papers" for killing flies are sheets of paper saturated with sweet solutions or pastes of arsenic. Single sheets have been examined which contained 10 grains of arsenic trioxid available for the poisoner. In the summer of 1915, 22 cases were reported² of accidental poisoning of children from this source. Of these 8 were fatal. It is deemed probable that other cases were unrecognized because the symptoms were mistaken for *cholera infantum*. "Fly-powders" have been made by pulverizing the mineral arsenid of cobalt. "Buffalo carpet-moth annihilator," intended to be dusted over the carpet, is a powder containing arsenic. White arsenic is often mixed with a dough of flour or corn-meal and distributed in cellars and pantries to kill mice. The most extensively used domestic vermin-killer is "Rough on Rats," a mixture of a little lampblack with white arsenic 70 to 80 per cent. and barium carbonate 30 to 20 per cent. The composition varies so much at times as to reverse this proportion of the two active ingredients. It is a gray powder put up in packages and procurable in every drug-store without restraint or legal registration. In this country a large number of suicides and some homicides have been caused by this agent. Among the means for wilful death it appears to be our national favorite. It is cheap, knowledge of its deadly properties is common, and there is every facility for purchasing it under the excuse of killing vermin. It is much to be desired that our state and municipal legislation relative to the sale of arsenical commodities should be shaped after the pattern of other civilized countries. Some provision should be made in the laws of every state which would require apothecaries to keep an arsenic book for recording sales of this poison, and which would forbid the sale of arsenic in any shape for the purpose of destroying vermin or for the embalming of dead bodies.

To overcome the gypsy moth, twig borers, and other insects, a

¹ See also Giordano, Ann. di. med., November, 1916, ii, 319. Legge, Jour. Ind. Hyg., 1920, 2, 130.

² Editorial, Jour. Mich. State Med. Soc., 1915, xiv, 580.

suspension of the white precipitate lead arsenate, Pb_2AsO_4 , or of calcium arsenite is sprayed over orchards and other food plants. "Arsenical balls" are given by grooms to improve the coats of horses. A leakage from a tin of arsenicated liquid "weed killer" contaminated a barrel of sugar in contact with it and thus caused an outbreak of vomiting and gripes in 20 households of Haslemere, England.¹ Some kinds of white enamel-ware and some glass contain arsenic. It has been found in the silk lining of coat sleeves, the glazed leather lining of hats, the brown paper lining of carpets, and the black cambric lining of furniture. It is sometimes present on the glazed paper and cardboard used for boxes, playing-cards, note-paper, and fancy wrappers for candy lozenges. At one time arsenical pigments were extensively used for coloring wall-hangings, lambrequins, cretonnes, chintzes, tarlatans, and artificial flowers and leaves. It has been alleged that numerous cases of slow poisoning have been traced to the arsenic from these sources pervading the atmosphere of dwellings. In making a diagnosis reliance has been placed upon the discovery of traces of arsenic in the urine of patients. It has been found there with surprising frequency.² Harding³ records a group of cases of chronic poisoning among the nurses at an asylum, traced to the green baize curtains, which were found to contain a large amount of arsenic. Kirschgässer⁴ has reported 26 cases of apparent poisoning from this source, in most of which, by collecting the urine for two days and evaporating it, he found arsenic present. Kuttner⁵ reported 6 cases (2 men and 4 women) of abdominal pain, diarrhea, and anemia in patients whose symptoms improved when absent from home, but recurred on return. The wall-paper contained arsenic and so did the urine when tested. He also found arsenic in cheap linoleums and thinks floor coverings may be the source of arsenical symptoms in puzzling cases.

The question as to the source of the arsenic is clouded by the liability to a fallacy from the presence of traces in such common materials as the illuminating-gas and even the filter-paper used by the analyst. It has been found in the urine of persons apparently healthy. Kossa⁶ has noticed traces of arsenic, copper, and mercury in the urine of numerous healthy individuals examined. He is inclined to think that these substances are not totally eliminated by the organism, and that in time the accumulated amounts might have an important bearing in certain medicolegal cases.

Hills⁷ analyzed the urine for arsenic in 180 cases, many of which were without symptoms of arsenical poisoning. He found arsenic in

¹ London letter, Jour. Amer. Med. Assoc., May 15, 1920, 74, 1413.

² A full account of some cases is given in Report of the Massachusetts State Board of Health for 1885; see also Chadwick, Boston Med. and Surg. Jour., 1887, cxvi, 129; Smith, *ibid.*, cxvii, 476.

³ Lancet, 1892, i, 525.

⁴ Vierteljahresschr. f. ger. Med., 1868, new series, ix, 96; see also Elzas, Nederl. Tijdschr. v. Geneesk., 1921, i, 2154.

⁵ Berliner klin. Woch., 1912, xlix, 2122.

⁶ Wien. klin. Rundschau, 1896, 10, 573.

⁷ Boston Med. and Surg. Jour., 1894, cxxxi, 453.

75 per cent., showing coincidence, rather than causation, of disease. The process of elimination by the kidneys was extremely slow. The daily amount averaged less than 0.01 mg. a liter of urine. In some cases as many as eighty days elapsed before arsenic disappeared from the urine. The use of Paris green and lead arsenate as an insecticide in gardens, and the presence of arsenic in coal-gas, may be sources from which minute traces are derived in unsuspected ways. Ayers reported¹ a case of a farmer's wife who, five years before, had sprayed fruit orchards and eaten fruit newly sprayed with an insecticide, probably arsenical. Ever since she had suffered, intermittently, presenting the clinical picture of chronic arsenical poisoning. Arsenic, 0.000329 per cent., was found in the urine, and minute amounts in the wall-paper and well-water. The chief source was probably dust from Paris green used for potato insecticide and stored in a box in the kitchen.²

Making all allowances for sources of error, it is clear that cases do occur of domestic poisoning presenting characteristic symptoms and yielding unmistakable proof of arsenic in the urine. The theory of the gaseous form of the poison has received much support from the experiments of Gosio and Sanger. Gosio's experiments at the Public Health Laboratories at Rome (p. 229) proved that a volatile arsenical compound was produced by certain common molds growing in contact with arsenicated substances such as might be used in wall-papers.

Professor Sanger³ and others have repeated Gosio's experiments and substantiated his results. He found that, with moisture, a temperature between 60° and 95° F. (15° and 35° C.), a supply of oxygen, and a small amount of arsenic, there was a development of a volatile product containing arsenic. Biginelli⁴ confirmed by Massen⁵ proved it to be di-ethylarsin— $\text{HAs}(\text{C}_2\text{H}_5)_2$. Gosio's discoveries have been verified by numerous investigators in many lands. While *Penicillium brevicaulis* is the mold yielding the best results, Schmidt⁶ found 13 species of mold acting similarly when grown on sour paste. Among these are *Mucor mucedo*, *Aspergillus vivens*, and *Penicillium glaucum*. Some investigators who wrongly assumed that the product would be arsenuretted hydrogen and limited their inquiry to this agent, have had negative results. In the present state of knowledge no wall-paper containing as much as 0.1 grain of arsenic in a square yard can be considered as harmless.

In Common Pigments.—Both accidental and intentional poisoning occur from the use of the pigments described below:

"Scheele's green" (copper arsenite, CuHAsO_3) contains 52.8 per cent. of arsenous acid. A bright-green paint is made by mixing this with the basis of oil-paints and of water-colors. Although the public is warned as to the deadly character of this pigment, it is still much

¹ Jour. Amer. Med. Assoc., 1918, 71, 2122.

² See also Putnam, Boston Med. and Surg. Jour., 1889, cxx, 235, 240, and 253; *ibid.*, 1890, cxxii, 421; *ibid.*, 1891, cxxiv, 623.

³ Proc. Amer. Acad. Arts and Sci., 1894, xxix, 112.

⁴ Atti, R. Accad. dei Lincei, 1900, 9, ii, 210, 242.

⁵ Arb. d. Kais. Gesundheitsamte, 1902, xviii, 475.

⁶ Dissertation Erlangen Univ., 1900.

used for giving color to wax tapers, toys, book-covers, artificial flowers, oil-cloth, calicoes, cretonnes, and tarlatan. An equivalent green color and one much less injurious can be made by mixing Prussian-blue and chrome yellow.

"*Paris green*" (copper aceto-arsenite, Schweinfurth-green) is a color made by mixing the acetate of copper with the arsenite. It contains over 50 per cent. of arsenic. There is an enormous consumption of this compound as an application to the potato plant to rid it of the Colorado beetle. Used on the tops, this does not affect the edible tuber under ground. The same practice upon the tobacco-plant is far from innocent, as the leaves here are the parts to be used. It is often taken by suicides, but its color usually prevents its criminal use, though occasionally accidental death has been caused by it. The inspectors of the N. Y. State Industrial Commission¹ investigated many toxic cases in workers producing Paris green. The dust inhaled and that lodged on the skin was gradually absorbed and caused arsenical intoxication. A cubic meter of the air of the works at 60° F. was found to contain 305 mg. of Paris green. Underclothing, 6 inches square yielded 1.1 mg. For self-protection workers in arsenical pigments and lead arsenate should plug the nose and ears with loose cotton, smear the face and hands with a simple ointment, take a full shower-bath, and change clothing at the end of the day's work.

Realgar (As_2S_2); *Orpiment* (As_2S_3); "*King's Yellow*."—The first of these arsenic sulphids occurs in ruby-red crystals containing 70 per cent. of arsenic; the second, containing 61 per cent., is a yellow powder which, by mistake, has sometimes been substituted for the harmless vegetable pigment, turmeric. The action is similar to that of white arsenic.

Arsenic in the Soil.—Some soils naturally contain arsenic in an insoluble iron compound. Headden² has found that other virgin soils yield traces to water as a solvent. After the use of "superphosphate" as manure, arsenic may be imparted by the impure sulphuric acid used in its manufacture. Paris green, sprinkled to kill bugs on the plants of potato, cabbage, or beets, add some to the soil. Lead arsenate and calcium arsenite as insecticides sprayed on orchard trees furnish a soluble fraction to the ground and the rootlets absorb it. In a number of years the soil of sprayed orchards is ten to twenty-eight times stronger in arsenic than was the virgin soil. Headden³ has also shown that potatoes, turnips, beets, oats, alfalfa, apples, pears, and the flesh of cattle grown on such a soil have all given signs of arsenic; that persons eating freely of apples from sprayed trees secrete urine showing arsenic; and that from such food plants and meats the human body may get while alive the trace often found postmortem, even if the arsenic-enriched soil does not supply it to the corpse after burial. In cities, in those states in which its use is not prohibited by law, it is often the custom for undertakers to embalm corpses by pumping a solution of

¹ Special Bull. 83, N. Y. State Dept. Labor, July, 1917.

² The Occurrence of Arsenic in Soils, Plants, Fruits and Animals, Proceedings of the Colorado Sc. Soc., vol. ix, p. 345.

³ Loc. cit.

sodium arsenate through the nostrils into the stomach, trusting to the high diffusibility of that salt to carry it throughout the body. Experiments¹ show that in twelve days the arsenic may permeate the entire body, reaching the brain. It is probable that this same compound would eventually pervade the soil of the cemetery contiguous to a buried corpse. Ekeley's research² showed marked traces of arsenic in the soil very near a corpse buried in a soil originally arsenic free. The investigations of Marshall and Ryan³ proved that the arsenic of a putrefying corpse was not evolved in a gaseous combination.

ORGANIC ARSENICALS

In Therapeutics.—This is a group of arsenic medicinal compounds whose toxicity to mammals is much less than that of the mineral arsenicals. In proper doses the arsenic ion is held safely while in these combinations, and this led to the hope that thus the innocuous agent could be made to reach the protozoa of disease in the tissues, presumably more susceptible to it than is the human host. Some organic arsenicals, such as arsphenamin and its derivatives, liberate trivalent arsenic slowly while stored in the liver and other tissues, and thus for longer periods than the mineral arsenicals they maintain contact with the parasites. The arsphenamins are successful in overcoming the spirochetes which cause syphilis, relapsing fever, African sleeping sickness, and even some bacterial affections such as anthrax. It is very doubtful if the other members of this general group, notably those containing pentavalent arsenic,⁴ exercise any power over the protozoal parasites in doses and concentrations which are not lethal to the patient. Clinical observation⁵ has shown that sodium cacodylate has no control over human syphilis. Castelli's experiments proved that "arrhenal" (methyl-arsenic acid) and "mon-arsone" (ethyl-arsenic acid) had no action upon the trypanosomes and the spirochete infections.⁶ While their ratio of the minimal effective therapeutic dose to the lethal dose was about 1, with no margin of safety, the ratio for arsphenamin was 17 and neo-arsphenamin 28, the last two giving a sufficient margin for practical purposes. Some other arsenicals, "atoxyl" (arsanilic acid) and its acetyl derivative "arsacetin," whose potency as parasitocides promised well in the treatment of syphilis, were found to have dangerous by-effects. Hence these chemicals have been discarded from the list of antisyphilitics while the arsphenamin group grow rapidly in favor as comparatively safe members of this class.

¹ Witthaus, *Bulletin of Loomis Laboratory*, 1890, i, 38; see also *Section on Post-mortem Imbibition of Poisons*, p. 861.

² *Jour. Amer. Chem. Soc.*, 1913, xxxv, 483.

³ *Med. Bull. Univ. Penna.*, 1909, xxii, 180.

⁴ Voegtlin and Smith, *Jour. Pharm. and Exper. Therap.*, Baltimore, January, 1921, 16, 449. Schamberg, Raiziss, and Kolmer, *Jour. Amer. Med. Assoc.*, 1922, 78, 402.

⁵ Nichols, *Jour. Amer. Med. Assoc.*, February 18, 1911, 56, 492; *Jour. Exp. Med.*, 1911, xiv, 196.

⁶ Voegtlin and Smith, *Jour. Pharm. and Exp. Therap.*, 1920, xv, 475; 1921, 16, 449; Nichols, *Jour. Amer. Med. Assoc.*, 1921, lxxvi, 1335.

But they too lack something of entire safety. Exposed to the air they oxidize readily into more toxic products; their composition is not as uniform as safety requires, and for various reasons the biochemical agencies of the body occasionally split off the arsenic in fatal amounts from doses ordinarily deemed safe. The untoward reactions referred to in the literature give to them great importance in toxicology and emphasize the need for full consideration of their chemical behavior and their effect on the body.

Cacodyl, $2\text{As}(\text{CH}_3)_2$ (dimethylarsin), is a volatile, colorless liquid with a strong garlic odor and is poisonous.

Cacodylic acid, $\text{As}(\text{CH}_3)_2\text{O}_2\text{H}$, is a white crystalline substance, soluble, odorless, and comparatively non-poisonous, though it contains 54 per cent. of arsenum. In overdoses it causes the same symptoms as arsenic trioxid. To obtain a mild arsenical action on the system without local gastric irritation several cacodylates are used by subcutaneous injection.

Calcium cacodylate contains about 45 per cent. of arsenum in the form of cacodylic acid and is free from arsenite, arsenate, and monomethyl arsenate. A safe dose is 0.0045 gram ($\frac{3}{4}$ gr.) repeated once daily.

Iron cacodylate, $\text{Fe}[(\text{CH}_3)_2\text{AsO}_2]_3$, is a ferric salt of cacodylic acid containing about 42 per cent. of arsenum. A safe dose is from 0.015 to 0.1 gram ($\frac{1}{4}$ – $1\frac{1}{2}$ gr.).

Sodium cacodylate, sodium dimethylarsenate, "arsykodile," $(\text{CH}_3)_2\text{AsO}.\text{ONa} + 3\text{H}_2\text{O}$, is a white crystal or granular powder, faint odor of garlic, deliquescent, very soluble in water and alcohol. When anhydrous it contains 35 per cent. of arsenum. Owing to changes liberating the arsenic ion by the digestive juices when it is given by the mouth or rectum alarming symptoms may appear, such as garlic taste, edema of the eyelids, nausea, gastric pain, and thirst.¹ It is best administered hypodermically when the danger of toxic action is very slight.² It is usually given in doses of 0.02 to 0.12 gram ($\frac{1}{4}$ –2 gr.) by subcutaneous injection. Its therapeutic virtues depend upon the continuous action of the arsenic slowly dissociated from the cacodylic acid, and which according to Heffter³ amounts to 2 to 10 per cent. of the total content.

Toxicology.—That cacodylic acid and its salts may occasion the toxic effects of arsenic has been shown by Lebahn,⁴ Schulz,⁵ and Rabuteau.⁶

Arrhenal, neo-arsykodile, arsinal, is disodium-methylarsenate, $\text{CH}_3.\text{AsO}.\text{(ONa)}_2$. It contains one methyl group less than the cacodylate. Its arsenic content is 25.68 per cent. when crystallized. It is a

¹ Brit. Med. Jour., 1900, ii, 823.

² Dawes and Jackson, Jour. Amer. Med. Assoc., 1907, 48, 2090.

³ Arch. f. exper. Path. u. Pharm., 1901, 46, 230.

⁴ Diss. Rostock, 1868.

⁵ Archiv. f. exper. Path. u. Pharm., 1879, xi, 131.

⁶ Jahres. f. Thierchen, xii, p. 96; Comptes rendues Soc. de Biol., 1882, 7 S., iv, 491.

white, odorless, water-soluble crystal. It is medicinally and for the most part chemically interchangeable with sodium cacodylate. A dose of 1 gram was followed by vomiting and diarrhea, but no abdominal pain.¹ The average dose is about 0.1 gram ($1\frac{1}{2}$ gr.).

Elimination and Distribution.—In the cacodylates the very small proportion of active arsenic set free is oxidized, then partly eliminated by the urine, sweat, and feces, and partly retained. By experiments upon animals Dawes and Jackson,² found that the cadaver had inorganic compounds of arsenic deposited in the liver, muscle, and bone-marrow.

Detection.—Cacodylates, like other organic arsenicals, do not respond to the ordinary reagents and tests. Some of them are proof against the most potent oxidizers and reducers. Sodium cacodylate in solution is a very feeble electrolyte and does not give arsin at the cathode. With Marsh's test it forms no metallic mirror nor will it precipitate from acid solution with hydrogen sulphid unless previously decomposed by boiling with sulphuric acid for six hours. Fuming nitric acid does not oxidize it to arsenous or arsenic acid. The arsenic is not extracted by the method of Fresenius and von Babo. Bettendorff's test does not separate the arsenic even after evaporation with potassium chlorate in hydrochloric acid.

In the *urine* cacodylic acid can be detected by treatment with hypophosphorous acid (sp. gr. 1.15), and standing aside in a closed test-tube several hours. The strong garlic odor of cacodylic acid can then be recognized. Instead of free hypophosphorous acid, Bougault's reagent may be made by dissolving 20 grams of sodium hypophosphite in 20 mls. (c.c.) of water and adding 200 mls. (c.c.) of hydrochloric acid (sp. gr. 1.17). The sodium chlorid formed should be removed by filtration through a plug of cotton or glass wool.³

Arrhenal does not keep its hold on arsenic strong enough to prevent precipitation of yellow arsenic sulphid by hydrogen sulphid. If distilled with strong hydrochloric acid the arsenic chlorid is found in the distillate. A large amount gives a red-brown precipitate with Bettendorff's reagent. In the urine it does not separate arsin at the cathode in electrolysis. Hypophosphite of sodium or Bougault's reagent precipitates arsenic immediately, yellow brown without garlic odor.

For Quantitative Determination.—The cacodylates, as well as most of the other organic arsenicals, may be extracted from the tissues by the method of Vitali.⁴ Mix the finely divided tissue with water, acidify with tartaric or hydrochloric acid, and evaporate to dryness. Extract this residue two or three times with 90 per cent. alcohol, filter, distill off the alcohol from the filtrate, and use the watery residue for the further steps. Decompose the organic arsenical, which is in solution,

¹ LeRoy des Barres, Arch. gén. de méd., 1903, i, 1635.

² Jour. Amer. Med. Assoc., 1907, 48, 2090.

³ Jour. de pharm. et de chim., 1902, 6 S., xv, 527; Ibid., 1903, 6 S., xvii, 97; see also Engel and Bernard, Ibid., 1896, 6 S., iii, 413.

⁴ Boll. chim. farm., 1901, xl, 657; 1903, xlii, 641.

by heating with concentrated sulphuric acid, ammonium or potassium sulphate, and a little potassium permanganate. After the oxidation is complete, dilute the mixture, filter if necessary, and precipitate the arsenic with hydrogen sulphid as carried out with the ordinary inorganic compounds.¹ The most approved methods of estimating the arsenic in these organic arsenicals are those by titration with the technic of Lehmann or of Robertson (p. 262).

Arsanilic acid is derived from arsenic acids $\text{AsO}(\text{OH})_3$, by substituting anilin for one hydroxyl. Other compounds are made by similar substitution with anilin derivatives.

Arsacetin or sodium acetyl arsanilate, $\text{C}_6\text{H}_4(\text{NH}.\text{CH}_3\text{CO}).(\text{AsO}.\text{OH}.\text{ONa})$, is a white crystal; odorless, tasteless, and water soluble. It is not decomposed by heating for an hour at 130°C . and its solutions are stable even when boiled. It gives no reaction of arsenous or arsenic acid, and is less toxic than *sodium arsanilate* or sodium para-amido-phenyl-arsenic acid, $\text{C}_6\text{H}_4(\text{NH}_2).(\text{AsO}.\text{OH}.\text{ONa})$. This latter, sold under trade names, *Atoxyl* and *Soamin*, is a white odorless water-soluble crystal with an arsenic content of 23 to 30 per cent. It sets free arsenic very slowly, producing therapeutic effects in a continuous way.

Dose.—If given by the mouth atoxyl is decomposed by the gastric acids and poisoning may result. It is best given hypodermically in doses of 0.02 to 0.2 gram ($\frac{1}{3}$ –3 gr.) every other day, increasing to single doses of 0.65 gram (10 gr.).

Toxicology.—Excessive doses of atoxyl have caused toxic symptoms about one-fortieth in violence to those of arsenic trioxid. One of these is blindness from atrophy of the optic nerve. Milian² calls attention to congestion of the conjunctivæ as a premonitory sign of poisoning from arsenicals, warning of impending blindness. Its toxicity does not depend wholly on free anilin nor on free arsenic, but somewhat on the complex group. In the fatal case reported by Schlecht,³ a man who had 2.4 grams (36 gr.) in four hypodermic injections within eight days, died on the second day after the last injection with edema of the lungs and paralytic⁴ phenomena. The autopsy revealed such cardiac and hepatic degenerations as are seen in arsenic poisoning.

Elimination and Distribution.—Most of it is eliminated by the urine unchanged. Some is found in the feces. The cadaver of a poisoned dog⁵ showed inorganic arsenic in liver, kidneys, lungs, bile, blood, spleen, muscles, brain, and hair. Its violent action condemns it as a remedy except for the sleeping sickness of Africa.

Tests.—*Atoxyl* responds to the Marsh and Gutzeit tests and slowly to the Reinsch test. In weak acidulated solution it is not precipitated by hydrogen sulphid in the cold, but fully so when warmed. With

¹ See Section on Principles of Toxicology, p. 47.

² Paris Méd., 1921, ii, 303.

³ Münch. med. Wochenschr., 1909, lvi, p. 972.

⁴ See Rona and Bach, Biochem. Ztschr., 1920, 111, 166, for the mechanism of the action of atoxyl.

⁵ Bull. Soc. pharm., Bordeaux, 1908, xx, p. 443.

silver nitrate it does not yield the red arsenate of silver, but a white precipitate of silver arsanilate soluble in nitric acid or ammonia. It can be detected by the electrolytic method.

Arsenoferratin.—Sodium arsenoferri-albuminate is a compound of arsenic with ferri-albuminic acid. It contains ferric iron in an organic arsenical equivalent to 5 per cent. metallic iron and 0.06 per cent. arsenum.

Arsenotriferferrin is an iron arsenoparanucleate containing 16 per cent. of iron, 0.1 per cent. of arsenum, and 2.5 per cent. of phosphorus, all in organic combination.

Elarson.—Strontium chlorarsinobehenolate contains about 13 per cent. of arsenum. It is asserted that the arsenic, being in lipoid-like combination, is more acceptable to the tissues and less irritating to the alimentary tract than the other arsenicals. It is sold in tablets which contain in each $\frac{1}{128}$ grain (0.0005 gm.). It is whitish, amorphous, tasteless, insoluble in water, and slightly soluble in alcohol and ether. It is best taken after meals.

Arsindiphenylchlorid,¹ $\text{As}(\text{C}_6\text{H}_5)_2\text{Cl}$, "sneezing gas," was used in the World War to fill explosive shells. Its effect was to irritate the air-passages, causing violent sneezing, coughing, salivation, headache, vomiting, and substernal pain. The gas-mask could not be kept on, and the victim succumbed to the lethal gas that followed and was inhaled through the breach thus made.

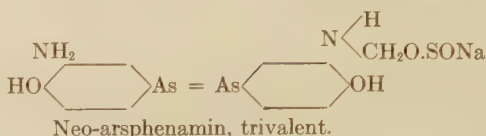
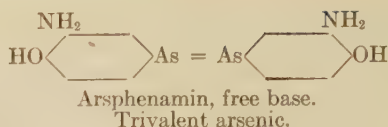
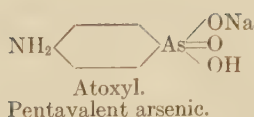
Arsinmethyldichlorid ($\text{As}.\text{CH}_3.\text{Cl}_2$) and **arsinethyldichlorid**² ($\text{As}.\text{C}_2\text{H}_5.\text{Cl}_2$) either alone or together, were lately employed as poisonous war-gases for filling shells. They are rapid and severe irritants to the eyes, nose, throat, lungs, and skin. Secondly, they are toxic from the arsenic content causing hemolytic jaundice, cramps, diarrhea, nephritis, and other arsenical symptoms.

Arsphenamin (U. S.), salvarsan (Germany), arsenobenzol (France), diarsenol (Canada), arsaminol (Japan). Under the trade name "606," Ehrlich³ gave the structural formula as 3-3' diamino, 4-4 dioxarsenobenzene dihydrochlorid. The name is officially contracted to *Arsenphenolamin hydrochlorid*, and is commonly sold in the United States as "arsphenamin." It corresponds to 31.57 per cent. arsenum in a trivalent form. Ehrlich held that pentavalent arsenic, such as exists in atoxyl and arsenic acid, acquires activity as a protozoal parasiticide only when it is changed to trivalent arsenic, such as exists in arsenites and the arsphenamins. This difference of the valence is shown in the graphic formulas given on page 252.

¹ Norris, Jour. Amer. Med. Assoc., November 30, 1918, lxxi, p. 1823.

² Ibid., p. 1825.

³ Deutsch. Chem. gesellschaft, 1912, vol. 45, 1, 756; Abhandlungen über Salvarsan, vols. i-iii.



Properties.—It is a pale-yellow, odorless powder microcrystalline, hygroscopic, decomposing readily in air, dissolving in water freely, imparting an acid reaction. When sodium hydroxid solution is added in the proportion of two molecules to one, the free base is precipitated. On further addition, aided by shaking, the precipitate redissolves in the strongly alkaline fluid. Arsphenamin may be marketed officially only in sealed colorless glass ampoules containing an inert gas.

Uses.—It is especially useful in the treatment of syphilis, but it is recommended also for other spirochetal diseases, such as frambesia and relapsing fever.

Administration.—Though it has been injected intramuscularly with good effect the intravenous method is preferred. It should not be given in its acid solution, hence at the time of administration the dose is neutralized with normal sodium hydroxid by a careful technic, which redissolves in alkaline excess the basic precipitate. After opening the sealed ampoule the contents should be used at once else oxidation sets in. The remnants and damaged tubes should be thrown away. Best results are obtained by persons familiar with the complex technic who can keep the patient under observation for some hours.

Dose.—While the dose should vary according to age, sex, and the condition of the patient, the average may be stated from 0.3 to 0.6 gram (5–9 gr.) for the first dose, which is repeated 4 to 6 times at intervals of one to two weeks. In syphilis it is customary to give a mercurial as an adjuvant alternately or in a follow-up course.

Fatal Dose.—In an epitome of the literature including his own experiments relating to the toxicity of arsphenamin, Roth¹ showed that the minimal lethal dose given to rabbits or rats intravenously averaged 0.1 to 0.15 gram per kilo which is equivalent to 7 to 10.5 grams (108–160 gr.) for a man weighing 70 kilos (150 pounds). The generally accepted therapeutic dose for man being 0.3 to 0.6 gram (5–9 gr.) gives such a large theoretical margin of safety as to confirm amply the conclusion of Pusey,² that though arsphenamin has serious dangers, they are remote if it be given properly. Corlett³ collected reports of 126 deaths from its use in such a number of cases as to rate the

¹ Bull. 113, 1918, U. S. Hyg. Lab., Washington, pp. 10–30; Reprint 688 from Pub Health Reports, 1921, p. 1990.

² Amer. Jour. Med. Sci., 1913, 146, 497.

³ Jour. Amer. Med. Assoc., 1913, lxi, 961.

mortality 1 death to 18,000 injections. Gennerich¹ advised that treatment should begin with 0.3 gram, and should not be increased to 0.6 gram which he regarded as the over-dosage, that has played a great part in lethal intoxications.

Toxicity.—In spite of precautions in the manufacture intended to secure purity and a safe arsenical, variable amounts of more toxic by-products may be developed.² Careless manipulations by the physician may create other organic arsenicals of higher toxicity, which may cause unlooked for complications. These dangerous products cannot always be detected by chemical analysis,³ but reveal their presence to biologic tests on rats before the drug is marketed. In fixing the standard of toxicity permissible the U. S. Public Health Service requires that 75 per cent. of the rats shall tolerate a dose of from 50 to 100 mg. per kilogram of bodyweight. Entire safety is not insured by this precaution, because toxicity is greatly influenced by the manner of preparation at the time of injection. The toxic effects sometimes encountered were ascribed by Ehrlich⁴ to the compound p. oxyphenylarsenoxid ("arsenoxid") formed by oxidation changes on exposure to the air. Not only is it customary to expose the agent for a short while at the time of clinical use, but some shaking is necessary to redissolve the precipitate formed when the drug is made alkaline with sodium hydroxid. Roth⁵ shook alkalized solutions of arsphenamin or plain aqueous solutions of neo-arsphenamin in air as is required by some marketed specimens to get a clear solution before injecting. This air-shaking for even thirty seconds rendered both drugs highly toxic to rats. The increased toxicity must be due to oxidation into "arsenoxid," since it was found that shaking neo-arsphenamin without access of air did not increase the toxicity.⁶ The solutions should not be made in an open mortar or a large beaker giving much contact with air. The symptoms in rats caused by "arsenoxid" were found by Hunt⁷ to be so characteristic as to be good evidence of its presence. He aerated alkalized solutions of different preparations of arsphenamin with variable results. Some increased in toxicity within an hour, others changed very slightly in this respect until after four hours aëration, but then more rapidly. However, the commercial *acidified* solution did not increase in toxicity after aëration for four hours. The toxicity due to "arsenoxid" could be lessened by adding sodium hydrosulphite as a reducing agent or by continued aëration at a temperature of 45 to 60° C. This further warm aëration carries oxidation beyond "arsenoxid" to the

¹ Hamburg. med. Uebersee, 1914, 2, 55.

² See Christiansen, Jour. Am. Chem. Soc., 1921, 43, 2202.

³ Raiziss and Proskouriakoff, Arch. Derm. and Syph., 1920, 2, 280; also Raiziss and Gavron, Jour. Am. Chem. Soc., 1921, 43, 582; De Myttenaere, Magnus, and van Boeckel, Bull. Acad. roy. méd. Belg., 1921, 5 S., 1, 104; Hooper, Kolls, and Wright, Jour. Pharm. and Exp. Therap., 1912, 18, 133; Oliver and Yamada, Ibid., 1922, 19, 393.

⁴ Soziale Kultur u. Volkswohlfahrt, 1913.

⁵ U. S. Pub. Health Repts., 35, September 17, 1920, p. 2205.

⁶ Smith, M. I., Jour. Pharm. and Exp. Therap., Baltimore, 1920, 15, 279; see also Schamberg, Kolmer, and Raiziss, Amer. Jour. Syph., 1922, 6, 1.

⁷ Jour. Amer. Med. Assoc., 1921, 76, 853.

point of forming a compound less toxic than arsphenamin, namely, p-oxyphenylarsonic acid. Pomarel¹ believes that "arsenoxid" cannot be incriminated for the symptoms of shock as the blood-pressure drops in the nitritoid crisis, while "arsenoxid" apparently increases the blood-pressure. In some samples there was an impurity of unknown composition,² more toxic than arsphenamin and which caused symptoms different from those of "arsenoxid." This toxicity is unaffected by warm aëration or the action of sodium hydrosulphite. Smith³ experimenting on dogs thought that the toxicity of different commercial samples of standard strength varied considerably. All of six different brands including a German one, had the same value as trypanocids.⁴ This degree of uniformity in remedial value was signalized by Roth,⁵ who demonstrated that the standard American and Canadian made article is as safe as any other now marketed. The question arises: Why have all of them at times exhibited untoward reactions? To determine how far these are attributable to undue toxicity of the sample Lake⁶ made animal tests that led to the conclusion that these reactions were often due to unusual susceptibility of the animal and to failure to observe proper precautions in administration. As summarized, they were greatly influenced by: (1) health of the animal; (2) mode of preparing the solution; (3) technic of administration. Roth⁷ calls attention to the influence of the age of the recipient as a factor influencing the toxicity. Jacobsohn and Sklarz⁸ believe that the toxicity is enhanced by increasing the K ions in the blood. If these conditions were made uniform difference of toxicity in the products were relatively small. Almost always the untoward effects followed the use of arsphenamin in too concentrated a solution or in too rapid administration. In addition to the precautions usually enjoined, the dose concentration should be not more than 0.1 gram to 30 mls. (c.c.) of fluid and two minutes be the minimum time allowed for intravenous injection of each 0.1 gram. This necessitates 30 to 180 mls. (c.c.) of solution for the usual dose and six to twelve minutes for the injection.

Toxic Reactions.—The sequelæ of the injections were classified by Martin⁹ as follows:

1. Slight untoward incidents in those whose tolerance is normal: vertigo, palpitations, nausea, disturbances of taste and smell.
2. Reactions in syndromes of discomfort and incapacity ascribed to allergy or acquired susceptibility or to toxicity of the solution.
3. Grave reactions, sometimes fatal, such as dermatitis exfoliativa, jaundice, hemorrhages, encephalitis, gangrene.

¹ Bull. méd., Paris, 1921, 35, 743.

² Schamberg, Kolmer, and Raiziss, Jour. Cut. Dis., 1917, 35, 286.

³ Jour. Pharm. and Exp. Therap., 1920, 15, 279.

⁴ Voegtlin and Smith, Jour. Pharm. and Exper. Ther., Baltimore, January, 1921, 16, 6.

⁵ Bull. No. 113, July, 1918, Hyg. Lab., Washington, D. C.

⁶ U. S. Pub. Health. Hyg. Lab., Amer. Jour. Syph., 1921, v, 96.

⁷ Amer. Jour. Syph., 1921, 5, 588.

⁸ Med. Klin., 1921, 17, 1327.

⁹ Jour. Amer. Med. Assoc., 1920, lxxiv, 1218.

4. Accidents, such as thrombosis, phlebitis, or infiltrations about the vein. At the time or just after receiving an intravenous injection the patient may have a crisis of redness of face, dyspnea, distress, cough, and precordial pain, or it may take the form of chill and fever. These immediate reactions, sometimes called "table" symptoms, which are usually slight, are sometimes grave, even fatal.

To explain them a theory has been broached that they are due to precipitates in the blood which may result in pulmonary embolism. Berman¹ regarded these precipitates as compounds of protein due to increased protein content in certain syphilitics and designated them as "nitritoid crises." In a study of these cases by Schamberg, Tokuda, and Kolmer² it was found that these precipitates were formed only when *acid* solutions of arsphenamin were added to serum, plasma, or defibrinated blood. Alkaline solutions of arsphenamin, that did not produce them in serum, did in some cases cause the immediate reactions when injected intravenously. The precipitates formed when blood and acid arsphenamin were mixed dissolved at once on addition of weak alkaline solution, showing them to be the drug arsphenamin itself and not protein. The serum of patients exhibiting these reactions after neo-arsphenamin did not form precipitates with that drug when mixed with it in a test-tube. It is deemed highly probable that these phenomena are dependent on the amount of alkali present in the solutions or in the blood. Variations in alkalinity might explain varying reactions of the patients. The danger of giving the drug in its acid form was illustrated in two sudden fatalities on the same day in the practice of a Toronto physician. They were reported³ as due to single doses of what was supposed to be neo-arsphenamin. The coroner's inquest⁴ established the fact that a concentrated unneutralized solution of arsphenamin had been administered by mistake. To prevent the immediate reactions which may attend the injection of even the neutral neo-arsphenamin Sicard and Paraf⁵ first inject into the vein 30 mls. (c.c.) of physiologic saline solution containing 0.60 or 0.75 gram of sodium carbonate. Milian, to protect against these shock symptoms, has been in the habit of adding sodium hydroxid to the solution of the arsenical.

Grave Symptoms.—Death may follow in a few days after a single large dose. The early acute prostration, nausea, and dysentery were attributed by Luithlen⁶ to the complex molecule acting as a whole and not to the arsenum ionized.⁷ After intensive medication with it the delayed effects are undoubtedly due to the dissociated arsenic. Among the most serious are nephritis, local paralysis, and loss of hear-

¹ Arch. Int. Med., 1918, 22, 127.

² Arch. Derm. and Syph., 1921, 3, 263; also Schamberg, Kolmer, Raiziss and Weiss, *Ibid.*, 1920, 1, 235.

³ Jour. Amer. Med. Assoc., 1921, 76, 5.

⁴ *Ibid.*, 1921, 76, 7.

⁵ Bufl. de la Soc. méd. des Hôp., Paris, 1921, 45, 11.

⁶ Zeitschr. f. exp. Path. u. Ther., 1913, xiii, 495.

⁷ *Ibid.*, Therap. Monats., Berlin, January, 1914, xxviii, 8.

ing and sight due to neuritis of the auditory and optic nerves. He thought the mishaps avoidable by not exceeding 0.4 gram in the dose and excluding all persons with depressed vitality from any cause except syphilis. He would not use it in secondary syphilis. The contraindications would include tuberculosis, chronic alcoholism, nicotineism, plumbism, severe gastro-intestinal and nervous diseases, and pregnancy. Studying 274 fatalities, including 41 in non-syphilitics, from injections of arsphenamin he concluded that the prompt primary symptoms were due to the whole organic arsenical. Later, after a variable interval, come others called secondary and due to the liberated arsenic.

Two cases of aplastic anemia in women were reported by Görke¹ in which the diagnosis was assured clinically and by blood count. They were attributed directly to the arsphenamin treatment, which has this effect, as rare as it is characteristic. Immediate withdrawal of the drug permitted recovery of one, but did not save the other from death. A robust man of thirty-eight years received² 0.5 gram of arsphenamin intravenously. Vomiting and diarrhea followed at once and death in convulsions on the fourth day. Fatal results have befallen feeble patients, especially those subject to diseases of the heart and vessels, fetid bronchitis, and advanced nervous syphilis.³

Distribution and Elimination.—The fate of the arsenic in the molecule was determined by Bornstein's⁴ examination of several cadavers of persons dying of intercurrent affections from two weeks to several months after injections of arsphenamin. His research on rabbits confirmed the findings on man to the effect that when the arsphenamin is injected it circulates in the blood entire for a short time only, and then arsenic separates, to be stored up in the liver, kidneys, and spleen. In one cadaver two weeks after the injection he found arsenic 6.5 mg. in the liver, 3.1 mg. in the kidneys, and 1.8 mg. in the spleen.

Elimination is completed very slowly. Traces of arsenic trioxid have been found in the urine in half an hour after a dose of arsphenamin, and they usually disappear only after one or two weeks. On the other hand, arsenic has been detected in the urine after the lapse of six months from the administration.^{5, 6} Bailey and Mackay⁷ reported on 25 cases of delayed toxic jaundice following arsphenamin treatment. Tests for arsenic in the urine made from twenty-four to one hundred and fifty-seven days after the last dose was given were all negative.

¹ Munch. med. Wochenschr., Munich, 1920, 67, 1226. See also Feinberg, Jour. Amer. Med. Assoc., 1922, lxxviii, 888.

² Brandenburg, Med. Klinik., Berlin, 1913, 27, 1065.

³ Almkvist, Münch. med. Woch., 1911, lviii, 1809; Fischer, Ibid., 1803; Kanengieser, Ibid., 1806; Ehlers, Klin. therap. Woch., 1911, xviii, 244; Gaucher, Sem. med., 1911, xxxi, 539; Westphal, Berlin, klin. Woch., 1911, xlviii, 973; Jorgensen, Med. Klinik., 1911, vii, 372; Martins, Deutsche med. Woch., 1911, 37, 240.

⁴ Deutsche med. Woch., Berlin, 1911, xxxvii, 112. See also Underhill and Davis, Arch. Dermatol. and Syphilol., 1922, 2, 40; Beeson and Albrecht, Ibid., 51; Mathieu, C. R. soc. biol., 1922, 86, 1029.

⁵ Bronfenbrenner and Noguchi, Jour. Pharmacol., iv, 1913, p. 333; Weiss and Raiziss, Arch. Int. Med., 1922, xxx, 85.

⁶ Young, Biochem. Jour., 1915, ix, 479.

⁷ Arch. Int. Med., 1920, 25, 628.

The urine was free from albumin and cellular deposits. This raises a doubt as to the jaundice being due to arsenic, as hepatic syphilis might have caused it.¹

Postmortem Appearances.—The intravenous injection of experimental animals with *acid solutions* of arsphenamin in lethal doses² caused histologic changes in the vascular system characterized by congestion, hemorrhage, and thrombosis. When the drug was given in single large *overdoses* of the *alkaline disodium arsphenamin* there were both vascular and tissue alterations of the liver, kidneys, spleen, and suprarenals. When the same alkaline drug was injected in multiple therapeutic doses the tissue changes were inconspicuous.

The general pathologic conditions when death is delayed are the same as when arsenic trioxid is given (p. 216). A research by Pearce and Brown³ showed that fatal doses of arsenic trioxid and of the organic arsenicals cause kidney lesions which are separable into two extreme groups. In one would be the *red* kidney of arsenic trioxid, congestion, hemorrhage, and capillary changes with only slight tubular necrosis. In the other such as are due to arsacetin and typical of the organic arsenicals—*i. e.*, a *pale* kidney, showing that tubular nephritis has dominated the congestion. The suprarenals were found the seat of changes in the capillaries, the cells, and also in the lipoid and chromaffin content.

Neo=arsphenamin (U. S.), neosalvarsan "914" (Germany), neo-diarsenol (Canada), neokharsivan (England), novarsenobenzol (France), neo-arsaminol (Japan). This is a combination of arsphenamin with sodium formaldehyd sulphonylate mixed with inert inorganic salts. Its constitutional formula is $\text{NH}_2\cdot\text{OH}\cdot\text{C}_6\text{H}_3\cdot\text{As} : \text{As}\cdot\text{C}_6\text{H}_3\cdot\text{OH}\cdot\text{NH}\cdot(\text{CH}_2\text{O})\text{OSNa}$. The graphic formula is given on page 252. Ehrlich devised it to prevent the easy oxidation of arsphenamin, which has two easily oxidizable amido-phenol groups. Three parts of neo-arsphenamin are about equal in arsenic content to 2 parts of arsphenamin. It has about 20 per cent. of arsenum.

Properties.—It is an orange-yellow unstable powder, changing rapidly in air to a dark brown color. It has a garlic odor, dissolves readily in water, making a neutral solution which turns brown on standing. It is marketed officially in hermetically sealed ampules containing the desired dose.

Uses.—It is more convenient than arsphenamin, as it does not require the addition of an alkali when dissolving it for injection. Its action and uses are the same as for that drug, though the ratio of the therapeutic to the maximal tolerated dose is more favorable to safety.

Dose.—The average dose for men is 0.75 gram (11.6 gr.), the maximal being 0.9 gram (13.9 gr.). For women 0.6 gram (9.3 gr.) is the average with 0.75 gram (11.6 gr.) as maximal. Solutions are made with freshly distilled sterile cold water or well-boiled water cooled at the tap. The solution is of not more than room temperature about 70° F. and is

¹ Miljan, Bull. mem. soc. méd. Hôp., Paris, 1920, 36, 226.

² Kolmer and Lucke, Archiv. Derm. and Syphil., 1921, 3, 483, 515, and 531.

³ Proc. National Acad. Sc., 1915, 1, 463.

injected immediately. Though it is easier to make this solution and when properly made it is better tolerated than arsphenamin, yet it has much the same toxicologic history and the same degree of skill and care is called for in its administration.¹

Fatal Dose.—Summarizing the literature and his own animal experimental results Roth² may be said to have proved that variation in the individual susceptibility is quite marked; that toxicity closely parallels the arsenic content and that neo-arsphenamin is less toxic than arsphenamin. The minimal lethal dose for rabbits and rats averaged 0.13 to 0.2 gram per kilo, which is equivalent to 9 to 14 grams (140–217 gr.) for a man weighing 70 kilo (150 pounds). Much smaller quantities have caused death as in the case observed by Hagerty,³ which presented symptoms of fatal arsenical poisoning following two doses of 0.6 gram each given with an interval of six weeks.

Toxicity is virtually the same in quality as that of arsphenamin, differing, however, in degree and in the lower frequency of alarming reactions at the time of administration. The research of Schamberg, Kolmer, and Raiziss⁴ demonstrated that the difference of toxicity is proportionally greater than that of the arsenic content. If the tolerated dose of arsphenamin (30 per cent. arsenic) be stated as 100 mg. per kilo then that of neo-arsphenamin (20 per cent. arsenic) is 200 to 300 mg. per kilo. It is probable that some of this decrease in toxicity is due to the change in the amino-groups which are factors in therapeutic potency also. Variations in the mixture of mono-substitution with possible di-substitution amino-groups may account for the irregularity of therapeutic and toxic effects.⁵ Macallum⁶ suggested that the neutral and alkaline derivatives of arsphenamin because of their amorphous character could not be made absolutely pure. A lack of definiteness and constancy in composition means more or less dilution with by-products.

Delayed Symptoms.—Policard and Pinard⁷ reported a case of old syphilis in a man of twenty-eight who, several weeks (fifty days) after three doses amounting in all to 1.05 gram of neo-arsphenamin, developed acute yellow atrophy of the liver, fatal in six days. The necropsy found in 100 grams of liver tissue $\frac{8}{1000}$ mg. of arsenic. Milian thought that the jaundice could not be attributed to the drug alone. He had treated 60 cases of this kind in which the jaundice had appeared several weeks after the arsenical course had ceased. All were rapidly cured by renewed treatment of the syphilis. In Brocq's⁸ opinion the drug given intravenously in large doses to kill spirochetes, passes by the hepatic artery to the liver and sets up toxic action there which

¹ See Roth, Reprint 700, Pub. Health Reports 1921, 2523; Jour. Amer. Med. Assoc., 1922, lxxviii, 1191.

² Bull. No. 113, 1918, U. S. Hyg. Lab., Washington, p.p 34–40.

³ Jour. Amer. Med. Assoc., 1913, li, 1294.

⁴ Amer. Jour. Med. Sci., 1920, clx, 188.

⁵ Raiziss and Falkor, Jour. Bio. Chem., Baltimore, March, 1921, 46, 209.

⁶ Macallum, Jour. Amer. Chem. Soc., 1921, xliii, 643.

⁷ Paris, Médical, January 8, 1921, 11, 42.

⁸ Bull. Méd., Paris, March 19, 1921, 35, 235.

later results in jaundice. The resisting power of the liver being reduced, the spirochetes have another chance to settle there and do further damage. In renewing the campaign against them he changes to mercury or to neo-arsphenamin subcutaneously.

Arsenic and Mercury Conjointly.—In the treatment of syphilis the associated curative power of both specifics is often resorted to with gratifying effect upon the disease, but later on, grave complications, and even fatalities, are fairly attributable to the retarded action of the poisons on the tissues especially of the kidneys and liver. A fatal case of jaundice in a woman after a single small dose of 0.122 gram (1.89 gr.) of neo-arsphenamin was reported by Hyman.¹ While the toxic symptoms and the postmortem findings pointed to arsenic, there was a history of previous intensive treatment by mercury. It was suspected that in this as in other fatal cases like it, the two poisons may have acted synergistically. Guibert² reported 2 cases of grave effects, 1 of them fatal. In both, treatment for secondary syphilis began with injections of mercury biniodid, followed by doses of neo-arsphenamin starting with 0.3 gram and increasing to 0.9 gram. One patient suddenly developed epileptiform symptoms and soon died. The other had high fever and erythema followed by desquamation. A noteworthy series of delayed poisonings was reported by Strathy, Smith, and Hannah.³ embracing 58 cases, 8 of which were fatal. The toxic symptoms developed after an interval averaging forty-three days from the last treatment with neo-arsphenamin. Jaundice figured in all of the 8 fatalities and in 39 non-fatal cases. Exfoliative dermatitis marked 8 cases. The medication had been intensive doses of neo-arsphenamin intravenously and intramuscular mercurial oil each once a week for seven or eight weeks. Most of the necropsies showed nephritis and hepatic atrophy. These serious toxic effects go to prove that the synchronous administration of massive doses of neo-arsphenamin and mercury is *extra-hazardous*. The kidney unduly overtaxed by the mercury becomes inadequate to eliminate the arsphenamin from the liver in which it remains stored until that organ is injured by the slow oxidation products one of which is free arsenic. When both drugs are called for it would seem safer to give the mercurial course after the arsenical and not conjointly with it.⁴ The margin of safety is in favor of a less intensive and a chronic intermittent method which may include both drugs in moderate doses given alternately at intervals of a week.

Elimination.—Gallonica⁵ reported that one hour after injection of arsphenamin intravenously, arsenic itself appeared in the urine. After neo-arsphenamin it was detected there in ten minutes.⁶ Both reached a maximum of this excretion at the end of the first day. After

¹ New York Med. Jour., 1920, 112, 496-8.

² Ann. de Dermat. et Syph., Paris, 1920, 6 S., i, 463.

³ Lancet, April 10, 1920, i, 80.

⁴ Schamberg, Arch. Dermat. and Syph., 1921, iii, 571.

⁵ Ann. de dermat. et syph., Paris, 1920, 8-9, 381.

⁶ See Scheffer, Ztschr. f. angew. Chem., 1921, 345, for a colorimetric method for determination of arsenic in urine and blood of treated patients.

intramuscular injection the maximum output of arsenic was on the second day. Given either way the last trace was not excreted until the sixth day. The total of arsenic eliminated by the urine was only a small part of that contained in the drug.¹

Postmortem Appearances.—These are not essentially different from those of arsenic except that there are no gross lesions of stomach and intestines. Kolmer and Lucke² by experiments on rabbits found that the histologic changes included vascular injury, cellular degenerations and necrosis. They involved the nervous and circulatory organs, the liver, lungs, kidneys, spleen, and suprarenals.

Sodium Arsphenamin, Sodium Diarsenol.—In this preparation the arsphenamin has been neutralized in advance, thus dispensing with the addition of sodium hydroxid at the time of administration. In it sodium has been substituted for the hydrogen of hydroxyl as shown in the structural formula: $\text{NaO.NH}_2.\text{C}_6\text{H}_3.\text{As} : \text{As.C}_6\text{H}_3.\text{NH}_2\text{ONa}$. The dose should be freely soluble in 15 to 20 mls. (c.c.) of distilled water by gentle shaking. If no undissolved particles appear it can then be diluted to the amount required for administration. As a precaution it is advised to filter the solution. These preliminaries with an unstable compound furnish the opportunity for oxidation impurities to form. It does not seem to be any more exempt than arsphenamin from the liability to contain hurtful by-products. The toxicology is virtually the same as for arsphenamin (q. v.).

Silver Arsphenamin—Argentum Arsphenamina (U. S.)—SILVER SALVARSAN, silver-sodium salvarsan, is said to be the sodium salt of silver-diamino-dihydroxy arsenobenzene. In it silver is supposed to be linked with sodium arsphenamin in a way not well understood. By its sponsors it is held that in this nearly black fluid the silver is not colloidal nor a suspension in a finely divided state. It is claimed that it combines the therapeutic activities of silver and arsphenamin, that it is more soluble than the latter alone, and that it continues in solution in the blood and body fluids for a long time.³ It is marketed in closed tubes to exclude air. The content of arsenic is about 22 per cent., that of silver about 14 per cent.

Dose.—In syphilis it is advised to give from 0.1 gram ($1\frac{1}{2}$ gr.) to 0.3 gram ($4\frac{1}{2}$ gr.) at intervals of twenty-four hours to four days. As a rule, from 8 to 18 intravenous injections are needed.

Uses.—There is a conflict of opinion as to its relative efficiency in the treatment of syphilis. On the one hand, some maintain that it destroys the spirochetes in doses one-half as large as those of arsphenamin and representing so much less arsenic that one keeps well within toxic limits.⁴ On the other hand, in the opinion of Schlotz,⁵ it does not offer definite advantages over arsphenamin.

¹ In this connection see Kohn-Abrest, Sicard, and Paraf, *Comptes Rend.*, 1921, 172, 301.

² *Arch. Dermat. Syphil.*, 1921, 3, 483, 515, and 531.

³ Kolle and Ritz, *Deutsche med. Woch.*, 1919, 45, 481; *Ibid.*, *Zent. Biochem. Biophys.*, 21, 240.

⁴ Rille and Frühwald, *Münch med. Woch.*, October 24, 1919, 66, 43.

⁵ *Deutsche med. Woch.*, 1920, 46, 884.

Toxicity.—Parounagian¹ reported that in his experience it was attended by no immediate "nitritoid crises," and such ill-effects as showed later were uncommon and not grave. A few patients so treated had mild headache, chill, nausea, vomiting, and gastric disturbance. At no time was mercury used conjointly. German literature mentions minor accidents, such as icterus and argyria. Any solution leaking outside the vein into the surrounding tissue had serious local results. Being amorphous, it lacks certainty as well as stability of composition. Nageli² noted that some lots of it induced toxic by-effects of angio-neurotic character. Corisa and Bejarano³ found that, as a rule, there was no immediate reactive fever, but they noted some disadvantages. As many as fourteen injections are usually needed for syphilis. To them the technic was difficult. In some instances at the site of injection there was increasing pain with formation of nodules and infiltration. Accidental periphlebitis and thrombosis have sometimes occurred.

Determination of Content of Silver and Arsenic.⁴—Place 0.2 gram in an Erlenmeyer flask and submit it to the Lehmann process (p. 262) through the stage of digestion. To the solution, still hot, add cautiously dilute hydrochloric acid to precipitate silver chlorid. Through a tared asbestos Gooch crucible filter off the silver chlorid, wash, and weigh. From the weight of chlorid calculate the percentage of silver, which should be about 15 per cent. The filtrate is put through the Lehmann process to the end of determining the arsenic content, which should be about 20 per cent.

Detection of Organic Arsenicals.—Ganassini⁵ asserts that cacodylic acid, methyl arsonic acid, and neo-arsphenamin produce in the exit-tube of the Marsh test (p. 225) a typical yellow ring. The *cacodylic acid* ring is orange colored (erytharsin), is formed only when the exit tube is heated at 335 degrees, and is characterized by dense white fumes. If the heat be discontinued and the gas be passed into Bettendorff's stannous chlorid reagent it does not yield a yellow precipitate.

Methyl arsonic acid forms an orange-colored ring at 335 degrees also, but without dense white fumes. Passed cold into Bettendorff's reagent it gives an abundant yellow precipitate.

Neo-arsphenamin gives a lemon-colored ring (As_2S_3), but only when the exit tube is heated to a high temperature. It is distinguished by not turning black on prolonged heating and by dissolving readily in ammonium hydroxid.

Arsphenamin shows positive reactions for arsenic with the Reinsch, Marsh, Gutzeit, and Gosio tests, but is negative to Bettendorff's test, and does not give a precipitate with hydrogen sulphid. Ferric chlorid solution gives with aqueous solutions of arsphenamin a brownish-violet color, which gradually changes to a dark red. Silver nitrate

¹ Arch. Dermat. and Syphil., 1921, 3, 333.

² Schweiz. med. Woch., February 26, 1920, 50, 9.

³ Arch. Derm. Syphil., 1921, iii, 465.

⁴ New and Non-official Rem., Jour. Amer. Med. Assoc., May 7, 1921, 76, 1312.

⁵ Boll. chim. farm., 1919, 58, 385.

solution added to an aqueous solution of arsphenamin acidified with dilute nitric acid yields a dark yellow precipitate, which rapidly becomes black.

Estimation of Arsenic in Organic Arsenicals.—Several procedures of approved merit have been in use in recent years, in the more practical of which the arsenic is first oxidized or reduced by digesting the material with suitable reagents and then estimated by titration with iodine. Ewins¹ imitates the Kjeldahl nitrogen method and thereby entails a loss of arsenic by volatilization during the digestion. The results, as a rule, are relatively low. A short cut is the Lehmann method as modified by Rogers,² in which the sample is oxidized with concentrated sulphuric acid and ammonium persulphate. The arsenic is extracted as arsenic acid for the actual analytical analysis.

Lehmann's method³ is approved by Myers and Dumez⁴ as follows: Weigh out accurately about 0.2 gram of the substance and transfer to a 200 mls. (c.c.) Erlenmeyer flask, preferably with a glass stopper. Add 1 gram of powdered potassium permanganate and 5 mls. (c.c.) of dilute sulphuric acid and let it stand for ten minutes. During this time rotate the flask frequently. Now add 10 mls. (c.c.) of concentrated sulphuric acid in portions of about 2 mls. (c.c.), rotating the flask after each addition. When the reaction has ceased, add carefully about 5 to 7 mls. (c.c.) of hydrogen dioxid solution, just sufficient to dissolve the brown precipitate, avoiding any great excess. Dilute the liquid with 25 mls. (c.c.) of distilled water and boil over gauze for ten minutes to remove the excess of hydrogen peroxid. To obviate the liability of a brown coloration if it be boiled down too far, the last trace of hydrogen dioxid can be removed by addition of a drop or two of 1 per cent. solution of potassium permanganate, clearing up the pink color by adding oxalic acid solution in slight excess. After diluting with 50 mls. (c.c.) more of distilled water, the solution is cooled and 2.5 gram of potassium iodid is added. The flask is stoppered tightly and stood in a cool place for one hour. Finally the freed iodine is titrated with N/10 sodium thiosulphate volumetric solution without using the starch test solution as an indicator. One mil. (c.c.) of N/10 sodium thiosulphate solution is equivalent to 0.003748 gram of arsenum.

Robertson's Method.—A two hours' method is that of G. R. Robertson,⁵ in which the substance is oxidized with a mixture of nitric and sulphuric acids and then freed from nitrous compounds by use of ammonium sulphate, reduced with hydriodic acid and titrated with standard iodine. The details are as follows: About 0.2 gram of the substance is weighed into a 150 mls. (c.c.) Pyrex Erlenmeyer flask and 5.5 mls. (c.c.) of concentrated sulphuric acid poured on it; then 1 mil. (c.c.) of fuming nitric acid is added and the flask set on a hot plate. The water in a similar flask beside it on the plate should boil actively, showing a temperature

¹ Jour. Chem. Soc. (London) Trans., 1916, 109, 1355.

² Can. Chem. Jour., 1920, iii, 398.

³ Originally appeared in Apoth. Ztg., 1912, xxvii, 545.

⁴ U. S. Pub. Health Reports, June 21, 1918, 1003.

⁵ Jour. Amer. Chem. Soc., 1921, xliii, 182.

of the mixture of about 250° F. In about half an hour arsphenamin or any of its intermediates is oxidized. After one hour the flask is removed, cooled, and 10 or 15 drops of fuming nitric acid are added. The flask is replaced on the hot plate and oxidation completed in five minutes. One gram of solid ammonium sulphate is added, the vessel is shaken a few moments until the nitrogen escapes, and set aside to cool. When the mixture falls below 100° F. it is clear. Cooled under a faucet the solution is increased in volume to 60 or 70 mls. (c.c.) by adding water. The Gooch-Browning¹ procedure is now applied as follows: One gram of potassium iodid is added to the mixture with a few grains of porous clay plate. A simple bulb trap, such as an inverted 25 mls. (c.c.) flask with a side vent, is placed in the mouth of the Erlenmeyer flask. The outfit is now heated on the hot plate until the liquid has been reduced by boiling to 40 mls. (c.c.) (mark on flask). The material condensed in the bulb trap is now rinsed into the flask. A solution of 0.01 *N* sodium thiosulphate is dropped in until the iodine tint disappears and the solution is instantly diluted with cold water to 100 or 120 mls. (c.c.). It is now transferred to a 500 mls. (c.c.) Erlenmeyer flask containing 50 mls. (c.c.) of 4 *N*-sodium carbonate solution and the residual acid neutralized with sodium hydrogen carbonate, finally including a small excess of the latter. Starch solution is added, and the arsenite present is titrated with standard iodine solution. A convenient standard solution is 1 ml. (c.c.) = 0.002 gram of arsenic.

Extraction from Tissues.—Arsphenamin and neo-arsphenamin may be extracted from the tissues by the method of Vitali, as discussed under Sodium Cacodylate (p. 249), or by direct extraction of the tissues with acidified alcohol. After filtering and distilling off the alcohol, the residue may be submitted to the Lehmann or Robertson methods previously discussed. Instead of following these methods, one may submit the above residue to digestion with sulphuric acid and ammonium persulphate, as advocated by Rogers, which process yields the arsenic in the form of arsenic acid. This may then be determined by the usual processes for the estimation of inorganic arsenic (see p. 230).

ANTIMONY

(Chemical Symbol, Sb; Synonym, *Stibium*.)

Antimony is a brilliant grayish-white solid with a crystalline, metallic fracture, tasteless and odorless. When heated it volatilizes; at a higher temperature it burns to antimony trioxid (Sb_2O_3). It is used as an alloy in type-metal, Britannia-metal, brass, and bell-metal. Though the metal may not be poisonous, its salts are.

While poisoning from antimony was quite common in the middle ages, in our times it is comparatively rare. Cases have been reported (Lohmeier)² from inhalation, probably of the trioxid, in certain industries. Lozenges containing the same preparation were the cause of

¹ Gooch, *Methods of Chem. Anal.*, Wiley, 1912; Gooch, Browning and Morris, *Amer. Jour. Sci.*, 1900, 10, 150.

² *Wehnschr. f. d. ges. Heilk.*, 1840, 265 and 286.

poisoning in another case.¹ In modern toxicology but two forms figure to any extent, the trichlorid and tartar emetic.

Sulphurated antimony, a mixture of Sb_2S_3 and Sb_2O_3 , is employed in vulcanizing rubber. The India-rubber connections of the Marsh apparatus might thus contribute a trace of antimony unless care be taken to avoid the use of fittings made with this preparation. Subtle poisoning of a mild grade may occur from the presence of antimony in rubber nipples to milk bottles.² Miller³ found that some of the cheaper gray enameled cooking utensils contributed antimony to various foods. Acid substances like cider and cranberries dissolved out from 3 to 14 mg., spinach 10 mg., and even fresh milk acquired 3 mg. Some European countries forbid the use of antimony in the enamel on culinary ware. Rubber workers who handle the sulphid may suffer antimony poisoning.⁴ The gastric juice dissolves 8 per cent. of the crimson sulphid and 3 per cent of the golden sulphid.

Antimony Trichlorid (SbCl_3 ; *Butter of Antimony*) occurs as a strong solution of the chlorid in hydrochloric acid, and is employed in the arts as a *bronzing* liquid, in farriery, and in medicine rarely as an external application.

In the records of 10 cases of poisoning that have been studied,⁵ it is found that in the 5 fatal ones the dose was 2 ounces, while 2 that recovered took 1 ounce each. A woman of forty years died in less than two hours; in her stomach were found 8 grains of antimony and 0.1 grain of arsenic.

Tartar Emetic (Chemical Formula, $\text{KSbOC}_4\text{H}_4\text{O}_6$; Synonyms, *Tartarated Antimony*; *Stibiated Tartar*; *Antimony and Potassium Tartrate*).—This is a white crystalline powder with an acrid, disagreeable, metallic taste. It is made by the action of a boiling solution of cream of tartar upon antimony trioxid. It has been dispensed by mistake for cream of tartar and for tartaric acid. It is soluble in cold water, more readily in hot water, but insoluble in alcohol. Wine is used as a vehicle in *vinum antimonii*, the water of the wine acting as a solvent and the alcohol checking the formation of the molds, to which a simple aqueous solution is liable. It is present in *syrupus scillæ compositus* ("Hive Syrup") and in *unguentum antimonii*. In the reports of 124 cases,⁶ the suicides make up 6 per cent., the homicides 20 per cent., the remainder being accidental.

Symptoms.—There is a close resemblance between the symptoms caused by antimony and those produced by arsenic. While it occasionally happens that large doses (200 gr., Taylor⁷) do not cause vomiting, as a rule, nausea, retching, and vomiting come on within half an hour and continue as conspicuous features of the clinical picture, which

¹ Page, *Lancet*, 1879, i, 699.

² Bull. 96, Hyg. Lab. U. S. Pub. Health S., 1914, p. 56.

³ Jour. Home Econ., 1916, viii, 361.

⁴ Hamilton, *Chem. Trade Jour.*, 1919, 65, 365.

⁵ Witthaus, *Manual of Toxicology*, New York, 1911, p. 351. See Bell, *Brit. Med. Jour.*, 1922, 1, 917.

⁶ Witthaus, *Manual of Toxicology*, New York, 1911, p. 352.

⁷ Taylor, A. S., *On Poisons*, 1875, p. 443.

may be sketched as follows: In a few seconds there is an acrid and metallic taste, followed by a sense of constriction in the throat and pain in the stomach; frequent and profuse vomiting, sometimes of bloody material; diarrhea with watery discharges, sometimes involuntary, sometimes attended with tenesmus; fainting attacks and depression, characterized by a feeble and frequent pulse and profuse sweating; spasmodic contraction of the arms, fingers, and legs. In very grave cases the urine may be wholly suppressed, the temperature subnormal, the skin cyanotic, and death be ushered in by delirium, convulsions, and coma. There are exceptional cases in which no vomiting occurs for an hour, and others¹ in which drowsiness and powerlessness come on early, are succeeded by tetanic spasms, the other symptoms also being present, and later persistent enteritis with loss of the hair on recovery. In a case recorded by Dobie² coma was the prominent symptom, with death on the sixth day.

When antimony chlorid has been taken, to the symptoms of antimony poisoning are added those of the strongly acid liquid, which causes corrosion of the stomach.

Chronic Poisoning.—In most cases of homicidal poisoning from antimony, tartar emetic has been given in divided doses to invalids. The effects of the poison are thus mistaken for symptoms of the disease, and the crime may go undetected. The patient is seen to suffer from "sickness," loathing for food, which, if taken, is not retained, diarrhea, muscular cramps, physical and nervous prostration, weak pulse, and cold sweats.

In the case of Mrs. Pritchard,³ occurring in October, 1864, she was taken with frequent vomiting and low health, which became better when she left home and grew worse on her return. Her meals were sent to her by her husband. After eating she would vomit within an hour, rejecting solids and liquids. There were constant thirst, chronic diarrhea, and extreme depression. Violent cramps in the hands were a marked feature. Her cheeks were flushed, as from alcohol. Her life was prolonged for four and a half months, her husband, Dr. Pritchard, maintaining that her case was one of typhoid fever. Having been condemned, he confessed to the crime of poisoning. Small quantities of antimony were found in all the viscera and tissues; from the liver, kidneys, and stomach $4\frac{1}{2}$ grains were extracted. In the intestinal contents it was present in the dissolved state in which it was given just before death.

A study⁴ of a large number of typesetters working with an alloy containing lead 75, antimony 20, and tin 5 per cent., showed that typical lead-poisoning was rare but irequently a syndrome existed, marked by mental and muscular weakness, nervousness, neuralgia, insomnia, vertigo, headache, nausea, vomiting, and constipation. The clinical blood findings were not those of lead but such as were

¹ Morley, Brit. Med. Jour., 1876, ii, 492.

² Lancet, 1887, i, 773.

³ Edinb. Med. Jour., 1865, xi, 163.

⁴ Strumpf and Zabel, Ztschr. f. exper. Path. u. Pharmakol., 1910, lxiii, 242.

present in animals experimentally poisoned slowly with antimony. Antimony poisoning was further indicated by the presence of the metal in the stools revealed to Marsh's test. Absence from the works, fresh air, and plain food sufficed for restoration to health. After investigating the printing trades Hamilton¹ reported not finding antimony poisoning.

Fatal Dose.—The smallest dose that has proved fatal to a child is $\frac{3}{4}$ grain (48.5 mg.).² A healthy woman, aged twenty-five years, took the maximum medicinal dose, $1\frac{1}{2}$ grains (97.2 mg.), without effect, but a similar dose twenty-four hours later excited violent purging and vomiting, with death in thirty-six hours.³ Such cases cannot be considered as fixing the danger limit. Ten grains⁴ at one time would be a dangerous dose, but the same amount in broken doses would be still more so.

Recovery has followed a dose of 170 grains.⁵ As a rule, prompt emesis follows the administration of a large dose, and the effects are mainly local and not serious. If the poison be retained and absorbed, the vomiting center is indirectly involved, and purging, with extreme depression, becomes the prominent symptom. At one time it was considered good practice in acute inflammatory diseases to give doses of a grain at intervals to establish "tolerance." By the second day some patients would tolerate the drug without vomiting and purging, and "heroic" doses of 5 grains each could be given without inducing these effects. As much as 60 grains daily have been given in this way without disturbance of the stomach. The effects in such cases are mainly those of depression of the heart's action and of the nervous system.

Fatal Period.—A fatal result has occurred in an adult in seven hours. In the exceptional case reported by Taylor death occurred in a child in three-quarters of an hour. The fatal event may be delayed for several days, the average duration of life being twenty-four hours.

Treatment.—As a rule, the free vomiting induced by the tartar emetic is sufficient to evacuate the stomach. In the rare cases where it does not occur other emetics should be given, such as sulphate of zinc or mustard and water; or the stomach may be washed out with a mixture of hot water with the antidote, tannic acid; or a decoction of green tea or of some vegetable astringent—all these forming the insoluble tannate of antimony. When the stomach has been emptied, morphin should be given hypodermically to relieve pain, and the irritable stomach and bowels treated with suitable remedies. The depression of the heart must be counteracted with stimulants, aided by dry heat or mustard to the epigastrium and the extremities.

If antimony chlorid has been taken, the corrosive action on the stomach would cause a condition which would be aggravated by the mechanical irritation of the stomach-tube.⁶

¹ Chem. Trade Jour., 1919, 65, 365.

² Taylor, Guy's Hosp. Reports, 1857, 3 S., iii, 369.

³ Beau, Bull. gen. de Thér., 1856, li, 231.

⁴ Taylor On Poisons, etc., 3d ed., 1875, p. 448.

⁵ Carpenter, New York Med. Record, 1883, xxiv, 401.

⁶ Compare p. 30 in Section on General Principles of Toxicology.

Postmortem Appearances.—One of the victims of Dr. Pritchard, Mrs. Taylor, died from acute tartar-emetic poisoning, and the autopsy revealed nothing, although the poison was found in the viscera, urine, blood, and intestinal contents. Such a result is quite exceptional, most cases showing redness, swelling, ecchymotic patches, and perhaps ulceration in the gastro-intestinal mucous membrane. Sometimes the changes in the gullet and pharynx are profound, as in a case described by Blyth,¹ in which there was destructive ulceration of the membrane of the epiglottis and of the adjacent parts, exposing the muscular fibers of the pharynx. In a case recorded by Cook,² of poisoning from the corrosive antimony chlorid, after vomiting without blood the patient went into collapse and died in two hours. The gastric membrane was almost black from congestion.

In cases of chronic poisoning it is usual to find inflammation of the kidneys and liver.

Tests.—1. *Hydrogen Sulphid.*—A stream of this gas will precipitate orange-red antimony trisulphid (Sb_2S_3) when passed through any antimonial aqueous solution acidified with hydrochloric acid (No. 5, Plate 3). This orange precipitate is insoluble in ammonium hydroxid, but dissolves in the fixed alkalis, in ammonium sulphid, and in strong hydrochloric acid, especially when heated. A very characteristic reaction is obtained when this hydrochloric acid solution (after boiling to expel all trace of hydrogen sulphid) is diluted with excess of water. A white precipitate of antimony oxychlorid falls, which is soluble in tartaric acid.

Fallacies.—While this test is quite certain in simple solution, it may give a doubtful result in the presence of colored organic materials.³ These should be entirely destroyed to give a satisfactory verdict.

Delicacy.—A definite reaction can be obtained with 1 : 10,000 of a grain of antimony trioxid in 5 grains of solution.⁴

2. *Reinsch's Test.*—The method of performing this test has been described under the heading of Arsenic. If any precipitate forms when the suspected solution is acidified with hydrochloric acid, more acid must be added until the oxychlorid is redissolved. On boiling in it a strip of bright, pure copper-foil a film of metallic antimony will appear. If the amount is small, the film is violet. A larger quantity will give a surface like tarnished zinc, and if abundant, a black amorphous layer.

Fallacies.—Arsenic, mercury, and some other metals make similar deposits. To distinguish the nature of the metallic films the copper strip must be washed, dried, coiled, and heated in a glass tube open at both ends. Under this treatment antimony yields a white sublimate of antimony trioxid, which is usually amorphous, although sometimes showing crystals; arsenic gives a sublimate of octahedral crystals; mercury a sublimate of shining metallic globules; and other metals, as a

¹ Poisons: Their Effects and Detection, 4th ed., 1906, p. 609.

² Lancet, 1883, i, 860.

³ Reese, "Wharton Trial," Amer. Jour. Med. Sci., 1872, n. s., lxiii, 329.

⁴ Wormley, Micro-Chemistry of Poisons, 1885, p. 224.

rule, produce no sublimate. The antimony trioxid may be dissolved in weak tartaric acid and an orange-red precipitate be obtained by passing hydrogen sulphid after acidification with hydrochloric acid. Again, the film of antimony on copper may be identified by boiling it in a weak solution of potassium hydroxid, removing the strip at intervals to expose it to the air. If the solution of antimony thus made is acidified with hydrochloric acid, it will yield an orange-red precipitate with hydrogen sulphid.

Delicacy.—A distinct violet-colored deposit on the copper can be obtained from 1 grain of a solution containing $\frac{1}{20000}$ grain of tartar emetic,¹ or $\frac{1}{80000}$ of a grain of antimony trioxid.

3. *Marsh's Test.*—Under the Section on Arsenic details have been given for performing this test. If antimony be present, the gaseous terhydrid will be formed, which has not the onion-like odor of arsenic terhydrid. Its flame produces a black spot on cold porcelain, while a metallic mirror forms in the delivery tube if that be heated by Berzelius' method. These may be mistaken for the similar deposits made by arsenic. When treated with solution of chlorinated lime or chlorinated soda, the antimony deposit is insoluble, while arsenic dissolves. Yellow ammonium sulphid dissolves both, but on evaporation the solution of antimony sulphid leaves an orange-red spot soluble in strong hydrochloric acid, but insoluble in ammonia. The corresponding arsenic sulphid is yellow, insoluble in hydrochloric acid, but soluble in ammonia.

If the gas, instead of being burned or decomposed by heat as above, is passed into solution of silver nitrate, there is a black deposit of silver antimonid, Ag_3Sb . If arsenic is also present, it remains in solution and, by filtration, we can separate the two. The filtrate can be tested for arsenic. The antimony in the precipitate may be separated from the silver by dissolving in boiling weak hydrochloric acid. When filtered again and treated with hydrogen sulphid, the filtrate gives orange-red antimony sulphid.

*Delicacy.*²—With a small apparatus spots on porcelain are obtained from 50 grains of a fluid containing $\frac{1}{2000}$ grain of antimony trioxid, while a good deposit in the heated tube is yielded by the same amount of fluid containing $\frac{1}{10000}$ grain of antimony trioxid.

The *silver nitrate test* gives a still more delicate reaction, and can be obtained with only a few drops of the test solution, a satisfactory deposit of silver antimonid forming when there is present only $\frac{1}{80000}$ grain of tartar emetic equal to $\frac{1}{20000}$ grain of antimony trioxid.

4. *Zinc Test.*—The suspected liquid is put into a platinum dish and acidified with hydrochloric acid. On immersing a slip of pure zinc, the antimony, but not arsenic, is at once deposited on the platinum as a black stain, which can be removed later by nitric acid or by simple heat. The true nature of this stain is revealed by wetting it with nitric acid, drying at a gentle heat, and touching with a drop of dilute ammo-

¹ Wormley, *Micro-Chemistry of Poisons*, 1885, p. 227.

² Wormley, *Ibid.*, 1885, p. 230.

mium sulphid, when an orange-red color will be produced, due to the formation of antimony trisulphid.

Delicacy.—This test is stated by Fresenius¹ to be very delicate. In two minutes a brown stain will appear when the solution holds but $\frac{1}{100000}$ grain of antimony, a definite reaction showing in a quarter of an hour when the amount is only $\frac{1}{200000}$.

5. *Tin Test.*—If an antimony solution is acidulated with $\frac{1}{10}$ part hydrochloric acid and a slip of pure tin-foil is immersed in it, the foil turns black from a deposit of metallic antimony.

Detection.—*In Vomited Matters and Urine.*—Owing to the prompt action of tartar emetic, the stomach and bowels are usually quickly evacuated of the poison. A large part of that which is absorbed into the general circulation is rapidly eliminated by the kidneys, and hence the proportion stored in the viscera is relatively small. In cases of suspected chronic poisoning the vomited matters, the liquid feces, the urine, or medicinal mixtures should be subjected to analysis. For this purpose the material is acidified with hydrochloric acid, and the zinc test or Reinch's test applied. These respond even in the presence of organic matters. To another portion of the material, acidified with hydrochloric acid, tartaric acid is added; it is heated on a water-bath for half an hour, strained, filtered, and the filtrate treated with a stream of hydrogen sulphid for several hours. The precipitate, which may contain the sulphids of certain other metals and free sulphur, should be treated with strong hydrochloric acid and boiled as long as hydrogen sulphid fumes escape. The filtered solution may be tested with Reinsch's test, the zinc test, or Marsh's test, collecting the antimony in silver nitrate solution. In testing the urine, the total quantity for several days should be evaporated to a small bulk before being operated on.

Separation from the Tissues.—From the solid viscera most of the antimony can be extracted by mincing a portion and boiling it for an hour in water, 5 parts, acidified with hydrochloric acid 1 part. The strained and filtered solution may be tested by Reinsch's or the zinc test.

Quantitative Determination.—If it is desired to calculate the total amount of antimony, it is best to use the process for destruction of organic matter by hydrochloric acid and potassium chlorate given under the Section on Arsenic.² This being done, the mixed precipitate obtained by passing hydrogen sulphid through the acidified fluid is washed, treated with strong nitric acid, and evaporated to dryness. A small quantity of a strong solution of potassium hydroxid is added to the residue, it is filtered, evaporated to dryness, and fused. The potassium antimonate in this fluid is boiled with solution of tartaric acid, acidulated with hydrochloric acid, filtered, and saturated with hydrogen sulphid gas. The orange-red antimonious sulphid (Sb_2S_3) thus obtained is washed on a Gooch filter, dried in a water-oven, and the free sulphur and residual moisture which are always present expelled by heating in

¹ Qualitative Analysis, American edition, New York, 1915, p. 275.

² Consult also p. 46 in Section on General Principles of Toxicology.

an atmosphere of dry carbon dioxid. Of this residue, which has been converted to the black sulphid (Sb_2S_3), 100 parts represent 71.77 of antimony.

When the presence of other poisonous metals is suspected, the precipitate made with hydrogen sulphid is treated thoroughly with yellow ammonium sulphid and the solution filtered. The arsenic or antimony is present in this filtrate, while mercury, lead, and copper remain upon the filter to be examined by appropriate methods. The filtrate is evaporated, and the residue treated with nitric acid and potassium hydroxid to convert the metals into potassium arsenate and antimonate. If the presence of both metals is suspected, this mixture is put into the sulphuric acid and zinc Marsh apparatus and the gas passed through silver nitrate as long as a black precipitate falls. The arsenic will be in the solution, and is separated by filtration. The black antimonid of silver is collected on a filter, washed, boiled with tartaric acid, acidulated with hydrochloric acid, filtered, and the filtrate precipitated with hydrogen sulphid. Of the dried precipitate of orange sulphid, 100 parts represent 196.47 parts of pure crystallized tartar emetic.

Quantitative determination of antimony by the *Gutzeit* method is given on p. 232.

TIN

(Chemical Symbol, Sn.; Synonym, *Stannum*.)

Though poisoning from tin salts is rarely reported, there is sufficient evidence to prove that it does occur.

Putty powder, a higher oxid of tin, was the cause of death in the case of a chemist,¹ who, by mistake, used it for months in his pepper-box. The solder used for fruit-cans contains tin. This, as well as the tin surface, may be dissolved by the action of acid juices of fruits or the fatty acids of meat and cause toxic symptoms. In the case of canned meats, the danger from this source is slight. According to Rössing,² it is unworthy attention, as the compound formed is insoluble in the digestive juices. He thought that the traces found in canned meat and fish existed as oxid. According to Wirthle,³ it is sometimes a basic stannous chlorid and sometimes a sulphid. He found that the corrosion of the tin can increases slightly after the second year, but the amount is never anything but slight, even after four years. An official report on food products⁴ revealed the fact that canned, slightly acid, beans may contain 600 mg. of tin per kilo. The source appeared to be the tinned and soldered container, which yielded this metal to the beans in proportion to the time and temperature of storage. Although some of the metal may have been present in solution, some was probably colloidal, and most of it in some insoluble "oxid, hydrated oxid, or basic salt."⁵ If physiologic effects ever occur from the small amount

¹ Med. Press and Circ., 1894, n. s., 57, 450.

² Zeitschr. f. analyt. Chem., 1900, 39, 147; see also Schryver, Jour. Hyg., 1909, 9, 253.

³ Chem. Zeitung, 1900, xxiv, 263.

⁴ Street, Bull. 200, Conn. Exp. Sta., 1917.

⁵ Bigelow, Bull. 2, Research Lab., Natl. Canners Assoc., 1914.

of soluble tin in foods, the symptoms are so vague and subtle as to excite no suspicion of poisoning and the quantity absorbed so small as to escape detection in ordinary urinary analysis. In view of the rarity of reported cases, a doubt has arisen as to the absorption of tin when its compounds are taken into the gastro-intestinal canal by the mouth. Hygienic investigators¹ have settled this question so far as the soluble salts are concerned. They proved that when large daily doses of sodium stannous tartrate were fed to animals for a long period, although no tin appeared in the urine during the first week (which indicates that absorption was slow) it was present in this excretion in later weeks of persistent dosing as if the mucosa had undergone some change more favorable to absorption. That this absence from the urine in the first week was not due to delayed elimination was evident when in other experiments, appreciable amounts were excreted within a day after its intravenous introduction. It is probable that continued dosing with an irritant induced in time a degree of enteritis, shown by the experiments of Mayerhofer and Pribram,² to be more favorable to absorption of poisons than is the healthy condition. In a later research Salant³ fed cats tin tartrate and chlorid, 20 mg. per kilo of body weight, daily for three months without harmful effects. But moderately large doses, 30 to 50 mg. per kilo fed for two and five-tenth months caused loss of weight. Taken thus with food tin seems well borne by animals in perfect health; still, permission should not be given for the manufacture and sale of foods containing it.

Symptoms.—Tin salts act as gastro-intestinal irritants, causing sometimes a metallic taste, usually nausea, vomiting, abdominal pain, diarrhea, cyanosis, and collapse. Severe symptoms like these were seen in 4 cases described by Luff and Metcalfe,⁴ due to eating tinned cherries, the strongly acid juice in the can showing 3.2 grains of malate of tin to the fluidounce.

In an investigation by Ungar and Bodlander⁵ upon the lower animals it was shown that even the non-irritating salts given subcutaneously caused toxic symptoms like those of other metals which undermine the health, sometimes even causing death. They found tin in the tissues and the urine.

Treatment.—Emetics and the stomach-pump should be used first, followed by bland demulcent drinks, stimulants, and anodynes.

Tests.—*Hydrogen sulphid* yields with stannous solutions brown stannous sulphid; with stannic solutions, yellow stannic sulphid (No. 6, Plate 3).

Mercuric chlorid is reduced by stannous chlorid to a gray deposit of metallic mercury.

¹ Buchanan and Schryer, Local Govt. Bd. (Med. Dept.) Report of Inspect. Foods, London, 1908, p. 18; Salant, Rieger and Trenthardt, Jour. Biol. Chem., 1914, xvii, 265.

² Zeitsch. exp. Path. u. Therap., 1909-10, vii, 247.

³ Jour. Ind. Hyg., 1920, 2, 72.

⁴ Brit. Med. Jour., 1890, i, 833.

⁵ Chem. Centralbl., 1887, 58, 644.

Solutions of fixed alkalis give with stannous salts a white precipitate of hydroxid which is dissolved by excess, and on boiling is reprecipitated as black oxid. With stannic salts the white precipitate when dissolved is not reprecipitated by boiling.

Detection.—To extract the metal from the tissues and organic fluids they should be boiled for some time in water acidulated with hydrochloric acid, filtered, and the above tests applied to the filtrate.

Quantitative Determination.—Solid material is semiliquefied by digestion with concentrated nitric acid and then charred by sulphuric acid and heat. After cooling, digestion is resumed with more nitric acid until a clear solution remains and nitric acid is driven off. After passing hydrogen sulphid the stannic sulphid is filtered off and dissolved in ammonium polysulphid or potassium hydroxid. By adding acetic acid, tin is precipitated; it is then separated, dried, ignited, and weighed as stannic oxid, SnO_2 .

Illustrative Cases.—A. Jolles¹ reported motor and sensory disturbances in the lower extremities of a young woman whose lower extremities were at the same period stained yellow from wearing yellow silk stockings. More marked nervous symptoms like ataxia were noted a few weeks later simultaneous with wearing the stockings. The urine was albuminous, and gave the tin reaction for two months after the stockings had been laid aside. The stockings were heavily impregnated with tin chlorid to give them "body," and the absorbed tin had produced marked anemia. With the exception of hysteric symptoms, the patient recovered in a few months. Salzer² reported a male patient, aged fifty-nine, with tonsillitis, temperature 102.5°F. , and marked chilly sensations in the extremities. After the acute symptoms subsided, some sore throat, "coldness," and vague general pains with anemia persisted until the accidental discovery that the patient had been wearing for one month a lower artificial tooth plate made of Watt's metal (tin, 2 parts to bismuth, 1 part). Suspecting tin poisoning two analysts independently detected traces of tin in the urine and weighable amounts in the feces. Twenty-two days after discarding the slightly corroded tin tooth plate the metal was still present in the blood. After that none was detectable in blood, urine, or feces. The anemia gradually disappeared but complaints persisted of flushes and creepy chills.

Distribution and Elimination.—Schryver,³ gave 20 mg. of tin salts subcutaneously and collected 1.5 mg. of tin in 20 grams of brain and spinal cord. Salant⁴ and his co-workers observed that after an intravenous injection of tin salts, they disappeared from the circulation within two hours. Some of the metal was found in the urine, more in the feces, 25 per cent. was in the skin, and the liver showed about 5 per cent. of the amount injected. Elimination like absorption was

¹ Münch. med. Wchnschr., 1901, 48, 372; Wien. med. Presse, 1901, 42, 496.

² Jour. Amer. Med. Assoc., 1918, 70, 980.

³ Jour. Hyg., 1909, 9, 262.

⁴ Jour. Indust. Hyg., 1920, 2, 72.

slow, the main exit was by the gastro-intestinal canal; the kidneys though a subordinate channel were not unimportant.

CHROMIUM

(Chemical Symbol, Cr.)

Toxic effects have resulted from potassium chromate, from chromic acid, and from lead chromate. As the poisonous properties of lead chromate, "chrome yellow," are mainly due to the lead contained in it, they are properly considered under the compounds of lead.

Potassium bichromate occurs in orange-red crystals used by dyers and furniture-stainers, and in the manufacture of battery fluids. Operatives in chemical works find that in the shape of fine aerial particles it irritates the respiratory passages, sets up ozena, and causes eruptions and excoriations leading to chronic ulcers. A pharmacist at Breslau¹ by mistake used it instead of sulphur to make an ointment for the treatment of scabies at the public clinic for skin diseases. A number were severely poisoned and 12 died according to *Nederlandsch Tijdschrift*. The symptoms were burning pain and sometimes vomiting. Two had fever, bloody and albuminous urine. A number had unequal pupils and retinal hemorrhages, but the most threatening symptom was inhibition of the kidneys. No favorable influence was obtained by treatment which included venesection, diuretics, intravenous injection of sugar and even decapsulation of the kidneys. Brieger² reported that the poison was found in the blood, urine, feces, and gastric contents.

Chromic acid (CrO_3), chromic anhydrid, occurs in crimson prismatic needles, deliquescent, freely soluble, and in strong solution acts on organic matter with energy. Its only use in medicine is external, as a deep caustic to the tonsils and to papillary growths. When applied to fungous growths in the mouth a portion may be swallowed, as in the case reported by Tisne,³ in which a dentist used it too freely. It caused an acrid taste and burning in the throat, pain in the nucha, with persistent vertigo, abundant vomiting of a ropy green fluid, and great prostration, with eventual recovery. Chromium was found in the urine. Even its external use is attended with danger. This was shown in the case reported by White.⁴ One application of about 50 grains in $\frac{1}{2}$ ounce of water was made to the external genitals after removal of papillary vegetations. In twenty-seven hours the woman died in a state of collapse. Congestion of the kidneys and liver was found, and both organs contained chromium.

Symptoms.—When swallowed, the compounds of chromium act as gastro-intestinal irritants, with additional effects upon the central nervous system. They cause a disagreeable taste, vomiting, pain, diarrhea, collapse, unconsciousness, dilated pupils, very slow respirations, and muscular cramps.

¹ Jour. Amer. Med. Assoc., 1919, 73, 1590.

² Ztschr. exp. Path. Therap., 1920, 21, 393; see also Urban, Berl. klin. Wchnschr., 1919, 56, 363; Colden, Ibid., 365.

³ Jour. de Méd., Paris, 1887, 13, 61.

⁴ University Med. Mag., 1889, 2, 54.

Fatal Dose.—Maschka has described a case of suicide in fourteen hours from about 3 drams of potassium bichromate, while Macniven¹ has reported a case of recovery from about 3 drams, and Philipson² a case of recovery from 273 grains.

Fatal Period.—Death from 1 ounce has occurred in forty minutes.

Treatment.—Chalk or magnesia should be given to neutralize the acid. Milk may be administered or used to wash out the stomach with the pump or tube. Anodynes are indicated for the pain, cerebral and respiratory stimulants for the depression of the nervous system.

Postmortem Appearances.—In his research Pander³ found that chromic acid preparations were absorbed with great rapidity both by stomach and skin, and its elimination was mainly by the kidneys, but to some extent by the liver and bowels. In acute cases death was caused by respiratory arrest or central nervous disturbance. In the gastro-intestinal tract were found inflammation, ecchymoses, and swollen follicles. An early morbid change was parenchymatous nephritis; the spleen was shrunken and the blood altered.

Tests.—Soluble chromates yield with silver nitrate a red precipitate; with lead nitrate, a yellow precipitate; with boiling dilute sulphuric acid and alcohol, a green color.

Detection.—Having treated organic matters with hydrochloric acid and potassium chlorate, the liquid turns green from chromic chlorid. Ammonium hydroxid added to the filtered liquid in slight excess will yield hydrated chromic oxid as a precipitate, which, after washing and drying, can be converted into potassium chromate by fusing with potassium nitrate and carbonate. After dissolving the fused mass (which will be more or less yellow in color if chromium is present) in water and making slightly acid with acetic acid, the chromate can be detected by the tests given above.

IRON

(Chemical Symbol, Fe; Synonym, *Ferrum*.)

Iron is present in the body, notably in the blood-coloring matter, also in food, and is a frequent constituent in tonic medicines. It has no specific poisonous action on living matter, such as is shown by some of the heavy metals like antimony and mercury. The gastric and intestinal irritation caused by overdoses of its salts is due to the acid component and not to the metal. Sufficient evidence exists that at least two of its salts, ferrous sulphate and ferric chlorid, have toxic properties.

Ferrous sulphate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$), popularly known as “copperas” and “green vitriol,” occurs in coarse green crystals often covered with a brown, rusty coat. In an unsuccessful attempt at suicide⁴ a woman took 2 ounces on an empty stomach. Functional nervous disturb-

¹ Lancet, 1883, ii, 496.

² Ibid., 1892, i, 138.

³ Ibid., 1887, ii, 975; Arbeit d. pharm. Inst., Dorpat., 1888, ii, 39.

⁴ Hall, New York Med. Jour., 1883, xxxviii, 401.

ances soon appeared, but subsided in a day or two, while diarrhea and abdominal pain marked the course of a subacute gastro-enteritis which lasted more than a month.

Ferric chlorid (Fe_2Cl_6) occurs most commonly in the widely used preparation *tinctura ferri chloridi* or "tincture of iron," a brown acid liquid, frequently mistaken for harmless liquids of the same color. It has been taken in toxic doses as an abortifacient. In Martinique 4 cases of homicidal poisoning were caused by it at the hands of one person.¹

Symptoms.—When ferric chlorid has been given experimentally to the lower animals with food, it has been found harmless even in considerable doses. The same amounts given fasting and in alcoholic solution have resulted in death in from one to sixteen hours. It causes an inky, metallic taste, violent abdominal pain, vomiting, diarrhea, paralysis of the extremities, suppression of urine, convulsions, and death. The feces are blackened by the iron sulphid formed.

Fatal Dose.—One case has been reported of death after five weeks from a dose of the chlorid equal to $1\frac{1}{2}$ ounces of the "tincture of iron." An ounce² has caused vomiting and urinary symptoms. On the other hand, a man³ aged seventy-two recovered from the effects of 3 ounces of the tincture.

Treatment.—The alkaline bicarbonates or the carbonates dissolved in a large amount of water or milk may be swallowed or used to wash out the stomach with a pump or tube. The gastro-enteric symptoms should be treated by rest and anodynes.

Postmortem Appearances.—In one of the Martinique cases cited above a greenish-black, fur-like "mud" covered the tongue, esophagus, and stomach; swelling, congestion, and ecchymotic points were the changes noted in the liver and kidneys, and hyperemia marked the brain and its membranes.

Tests.—*Ammonium sulphid* causes a black precipitate of iron sulphid. It can be used after the metal has been extracted from the tissue with acetic acid. Redissolving the sulphid in nitrohydrochloric acid, the iron will yield to *potassium ferrocyanid* a blue precipitate. If the iron solution is almost neutralized with ammonia, then *ammonium sulphocyanid* will give a red color.

Detection.—Having digested the organic matters thoroughly in water acidulated with acetic acid, filtered, evaporated the filtrate to dryness, and incinerated the residue, the ash is treated with dilute sulphuric acid and the solution tested as above with ammonium sulphid and potassium ferrocyanid. Determination of poisonous amounts must rest upon the quantity found in the organs in excess of that normally present. The black fur on the mucous membranes and the stains on the clothing ought to yield significant amounts.

¹ Berenger-Feraud and Porte, *Annales d'Hyg. Pub.*, 1879, 3 S., i, 312 and 508.

² Taylor, A. S., *Principles and Practice of Medical Jurisprudence*, 6th ed., 1910, ii, 523.

³ Blyth, A. W., *Poisons, Effects and Detection*, 4th ed., 1906, p. 698.

ZINC

(Chemical Symbol, Zn.)

This is a bluish-white metal used in the arts in the form of sheet zinc, from which culinary vessels are made; also, under the name of "galvanized iron," as a plating on iron tubes or vessels. On exposure to moist air a white rust or film of oxid forms, which does not dissolve in water unless the water contains chlorids. The well-known fact that milk keeps sweet longer in zinc vessels than in pots is explained by the neutralization of lactic acid by the zinc, which is taken up as a lactate. Not only may milk thus be contaminated, but also vinegar, soup, olive oil, and alcoholic liquids. A plum marmalade prepared in a vessel coated with zinc was found by Salkowski¹ to yield 3.4 per cent. of zinc estimated as sulphate. The symptoms produced by articles of food thus contaminated are not grave. Salant and his co-workers² fed to rats and cats small amounts of zinc acetate and malate daily for four months, with no affection of the general health. But if introduced into the circulation directly it depressed the heart and affected the muscle of the intestines besides causing glycosuria and albuminuria. They conclude that while apparently well borne for some time, yet serious results may follow, and hence a caution is sounded against sale of foods containing even a small determinable amount of zinc.

Normal Zinc.—The heavy metals copper, arsenic, and zinc are found so often in human tissues and foods as to be considered relatively harmless there in minute proportions. From the blood stream mere traces of zinc are stranded for a time in the liver and other organs until the accumulations are weighable. One source is the "normal" zinc of oysters,^{3, 4} and other marine foods. If not so universally present it is at least common in cereals, milk, and eggs, of which each yolk⁵ gave an average of 1 mg. zinc. Samples of milk from different cows varied, but they averaged 4.2 mg. of zinc per kilo. Human milk exceeded cow's milk in its proportion of the metal,⁶ the colostrum showing less than later milk. Zinc may be an essential constituent of some forms of protoplasm and in milk and eggs may have an important function in nutrition.

Elimination and Distribution.—Like the other heavy metals zinc introduced directly into the circulation leaves the body mainly by the gastro-intestinal canal, though the proportion in the urine is relatively large.⁷ After intravenous injection it rapidly disappeared from the blood stream, 12 to 15 per cent. was recovered from the liver. It was present in the skin and muscles but not in the brain.⁸ A report of the results of examining the viscera of 22 victims of accidental death was

¹ Zentr. Biochem. und Biophysiol., 1918, 19, 345.

² Jour. Ind. Hyg., 1920, 2, 72.

³ Phillips, Dept. Marine Biol. Carnegie Instit., Washington, Pub. 251, 1917, 11.

⁴ Hiltner and Wichtmann, Zinc in Oysters, Jour. Biol. Chem., 1919, 38, 205.

⁵ Birekner, Jour. Biol. Chem., 1919, 38, 191.

⁶ See, however, Rost Med. Klin., 1921, 17, 123.

⁷ Salant, Rieger and Trenthardt, Jour. Biol. Chem., 1918, 34, 463.

⁸ Salant and co-workers, Jour. Ind. Hyg., 1920, 2, 72.

made by Ghigliotto,¹ who found the content of zinc oxid varied between 0.0015 and 0.0028 per cent. of organic tissue. After finding it in the human and the bovine fetus he thought zinc normal to animal organs. Giaya² made determinations of zinc contained in human viscera from 7 subjects, aged from three months to seventy years, and also the human fetus. Zinc was constantly present, the proportion increasing with the age. His experiments convinced him that zinc was not significantly toxic up to 0.05 gram per kilo of viscera weight. In proving zinc to be a constant constituent of the animal body, De Gramont³ identified it by the spectroscope when the amount was so small as to escape detection by the wet method. The feces and urine of many healthy persons in no way associated with zinc industries are found to contain zinc and copper. They are present also in many foods, such as meats, fish, eggs, bread, potatoes, and dried vegetables.⁴ Under present conditions zinc and copper are regular though possibly accidental constituents of the tissues of vegetables, animals, and man. It appears unavoidable to ingest these minute amounts which cause no perceptible injury either to the digestive apparatus or to other organs. Still no zinc nor zinc-coated vessel should be used in cooking, nor in storing foods that are acid or liable to acid fermentation, lest zinc salts be formed and swallowed in amounts sufficient to irritate the alimentary mucosa or do injury systemically.⁵ Zinc is freely soluble in all acids and even in water when it holds carbon dioxid in solution.

Poisonous Salts.—Of 90 cases of acute zinc-poisoning collected,⁶ 57 were in Great Britain and only 3 in the United States. All except two were caused by either of two salts, the sulphate and the chlorid. The sulphate was to blame in 29 cases, of which 9 were due to mistaking it for "Epsom salt"; 8 were suicidal, and 4 were homicidal. Zinc chlorid was the poison in 59 cases, of which 43 were accidental and 10 suicidal. The form used in 27 cases was "Burnett's disinfectant"; in 4 it was "soldering fluid."

Zinc sulphate ($\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$), or "white vitriol," is a freely soluble salt and occurs in crystals so closely resembling magnesium sulphate that it is often mistaken for it. The zinc salt is sometimes kept in the household as a prompt emetic for emergencies. "Epsom salt" is also a domestic remedy, and both are often kept in the same closet, in loose packages without labels.

These facts account for the frequency with which accidental poisoning occurs. In doses of 20 or 30 grains zinc sulphate will evacuate the stomach without causing much depression. This effect is so constant that, even after doses of an ounce are taken, recovery is the rule. When complete expulsion does not occur, it acts as a gastro-intestinal irritant, causing vomiting, purging and, secondarily, dangerous prostration. In

¹ Ann. fals., 1919, 12, 12.

² Comptes rendus d. l. Acad. Sci., 1920, 170, 906.

³ Ibid., 1037.

⁴ Rost, Die Umschau, 1920, 24, 201.

⁵ Rost and Weitzel, Zentr. Biochem. und Biophys., 1919, 21, 44, 422.

⁶ Witthaus, Toxicology, 1911, p. 782.

1 case there was neither vomiting nor purging, but death occurred in less than four hours from the depressing action on the nervous system.

Zinc chlorid (ZnCl_2) is a very soluble, deliquescent salt, present in "Burnett's disinfectant," also in the "soft injection" fluid used for preserving bodies for dissection.

A soldering fluid is made extemporaneously by dissolving zinc to saturation in hydrochloric acid. This fluid is used to cleanse the surface of metals, so that the solder can make a perfect joint. In the shape of fused caustic sticks the chlorid is used to transfix cancerous tumors, the effect being to disorganize the growth for a considerable area, as the salt absorbs water from the tissues and diffuses readily. It is sometimes applied as a paste by cancer quacks in so careless a manner as to cause death. Blyth¹ mentions a fatal case in which this external application to the breast produced general symptoms of poisoning by zinc, and the metal was found in the liver and other organs.

Symptoms from Zinc Chlorid.—The gastro-intestinal symptoms are those of a powerful corrosive—a metallic taste with instant burning pain in mouth, throat, and stomach. The act of swallowing is difficult and painful, and the salivary flow excessive. Violent vomiting begins immediately, often of bloody matters; purging supervenes, with tenesmus and bloody stools. Collapse may end in coma and death in a few hours. If life is prolonged, nervous sequelæ are common, such as perversion of the special senses, localized muscular spasms, muscular weakness, and aphonia. The local action may cause stricture of the gullet or pylorus, and also destruction of the glandular structure of the stomach, thus impairing digestion, so that inanition, extreme wasting, and even death may ensue.

Zinc Chlorid Burns.—In the process for preservation of railroad ties zinc chlorid is used as fungicide and fire-resistant. Handling the wet wood after this treatment causes dermatoses from tar and, in addition, multiple lesions on fingers, hands, forearms, and legs ascribed to the solution of zinc chlorid concentrated by evaporation.² A slight abrasion from any cause became the center of escharotic tissue sometimes very painful. When the "core" was removed and its place filled by sodium bicarbonate and petrolatum, the sore healed. The non-appearance of constitutional symptoms is explained by the absence of zinc fumes and dust. Prevention was achieved by wearing canvas overalls and lineolated canvas gauntlets.

Fatal Dose.—The prompt emetic action of zinc sulphate has brought about recovery after doses of 1 ounce; death has ensued from taking $1\frac{1}{2}$ ounces. The caustic action of zinc chlorid has caused death secondarily after several weeks from the administration of 6 grains. Von Csányi³ reports recovery of a child of two years following the drinking

¹ Blyth, A. W., *Poisons, Effects and Detection*, 4th ed., 1906, p. 690. See also Engelsmann, *Deutsch. med. Wehnschr.*, 1922, 48, 488.

² McCord and Kelker, *Jour. Amer. Med. Assoc.*, 1917, 76, 7.

³ *Jahrb. f. Kinderh.*, 1921, 95, 339.

of 5 grams of a 50 per cent. solution of zinc chlorid. Recovery has been brought about after a dose of 200 grains.

Fatal Period.—While death has occurred in about four hours¹ from administration of zinc sulphate without vomiting, and in another case from zinc chlorid, yet there are instances of death from the secondary effects of disorganization of the stomach and stricture of the gullet as late as one hundred and sixteen days after the dose.²

Treatment.—The efforts of the stomach at evacuation must be assisted by free drafts of warm water or warm milk. The stomach-tube may be used in the very exceptional cases when emesis is not prompt. The antidotes are milk, eggs, and the vegetable astringents containing tannin, represented by strong decoctions of green tea.

Postmortem Appearances.—The usual consequences of irritant poisoning, more or less intense, are to be seen—*i. e.*, congestion in the mouth, gullet, stomach, and intestines, areas of softening, ulceration, and even perforation. When death is due to secondary starvation, there is usually narrowing of the gullet, with thickening and corrugation. Jalland³ reported a case of death on the eighty-eighth day, in which the stomach, as a digestive organ, was practically obliterated. It was found to be a part of a mass of organized inflammatory products matting together the omentum, pancreas, liver, spleen, and diaphragm.

Industrial Poisoning.—"Spelter chills"⁴ is the condition caused by inhaling the fumes and ingesting the dust in the process of melting and vaporizing the impure zinc known as "spelter." It is characterized by chilly sensations, genuine rigors, pains in limbs and abdomen, rapid pulse, heightened temperature, irritating cough, prostration, nausea, and diarrhea. The chill is followed by exhaustion, sweat, and deep sleep. A metallic taste and anorexia last a while, but in the intervals of attacks the workers are not often incapacitated.

As zinc makes one-half of the composition of brass, it is responsible for the symptoms known as "brass founders' ague,"^{5, 6} occurring in workers exposed to the fumes and dust of brass foundries. About 70 or 80 per cent. have the chills, the others escape. Of 189 workers, 146 complained of some ailment traceable to their occupation; 45 had "brass chills." After continued exposure other affections supervened, involving lungs, digestive tract, kidneys, and nervous system. Longevity was relatively low; of 1761 men, only 17 were over fifty years old. To prevent these effects foundries should be equipped so that the workers do not inhale fumes or dust.

Pfender⁷ gave the name "brazier's disease" to attacks having a similar symptom-complex occurring in workers who by heat braze pieces of metal together. The fumes of molten zinc or brass caused

¹ Penfold, Austral. Med. Jour., 1883, n. s., 5, 340.

² Tuckwell, Brit. Med. Jour., 1874, ii, 279.

³ Ibid., 1887, i, 1387.

⁴ Riesman and Boles, Amer. Jour. Med. Sci., 1917, clii, 376.

⁵ Occupational Diseases, Illinois, 1911, Hayhurst report.

⁶ Amer. Jour. Med. Sci., 1913, cxlv, 723.

⁷ Jour. Amer. Med. Assoc., 1914, lxii, 296.

rigor with exhaustion as soon as the worker got into the open air. Sometimes there was a temperature of 101° F. followed by sweat. In the interval he appeared well; the body weight was reduced 18 pounds in a few months. It was the opinion of Hayhurst¹ that when brass or zinc is fused by gas flames it is probable that the vapor of zinc carbonyl is inhaled and absorbed in the air-passages. Owing to the presence of minute amounts of lead, arsenic, and antimony in some zinc ores these metals come under suspicion. Seiffert's² research led him to conclude that in zinc smelting these are not the cause of illness as often as is supposed. The dangers from zinc are real, though often underestimated. Even a slight daily absorption of it continuously will gradually derange health.

Tests.—1. *Hydrogen Sulphid Test.*—A stream of this gas precipitates white zinc sulphid from an alkaline or neutral solution, or a solution made acid by acetic acid. This precipitate is soluble in the mineral acids, but insoluble in acetic acid, the alkalis, and the alkaline sulphids.

2. *Ammonium sulphid* gives the same precipitate, the only white insoluble sulphid obtained by this procedure.

3. *Potassium ferrocyanid* can be used to distinguish zinc sulphate from magnesium sulphate and oxalic acid, both of which have been mistaken for it. White zinc ferrocyanid is thrown down from a solution containing zinc sulphate, but the two others yield no precipitate.

Detection.—Organic matters supposed to contain zinc may be digested at a gentle heat with dilute acetic acid, filtered, the filtrate concentrated, and the metal thrown down as sulphid by a stream of hydrogen sulphid. This precipitate, collected on a filter, is washed, dissolved in strong nitric acid, evaporated to dryness, the residue taken up with water, and precipitated as a hydratocarbonate by adding sodium carbonate and boiling thoroughly. Having filtered and washed the precipitate, it can be dried, ignited, and weighed as ZnO.

A small portion of the hydratocarbonate may be fused on platinum with a drop of cobalt nitrate. The zinc is detected by a green color resulting. In estimating the zinc content of foods where the metal in a sample is below 0.5 mg. Birkner³ found satisfactory the convenient *turbidimetric* method of Breyer.⁴

CADMIUM

(Chemical Symbol, Cd.)

Cadmium is seldom encountered in any of the arts except in zinc smelting. It is similar to zinc chemically and has like physiologic effects, but is more toxic. According to Kobert⁵ the sulphate is twice as poisonous as zinc sulphate. In toxic doses it acts as an irritant to stomach and bowels. When absorbed it is excreted by the same channel and the urine, thereby inducing chronic gastro-enteritis and nephritis

¹ Report on Occupational Diseases, Illinois, 1911.

² Chem. Zentr., 1918, ii, 305.

³ Jour. Biol. Chem., 1919, 38, 191.

⁴ In Scott's Standard Methods of Chemical Analysis, 2d ed., 1917, p. 487.

⁵ Erben, Vergiftungen, 1909, vol. i, 432.

besides degenerations of the liver and heart. It is a constant constituent of *calamine*, native zinc carbonate in the proportion 0.5 to 1.5 per cent. In smelting zinc from this ore the more volatile cadmium distills in the first fumes, often before the retorts are closed by connection with the pipes. Hence in the livers of spelter workers cadmium sometimes exceeds the quantity of zinc found. Stephens¹ reported symptoms that he at first thought due to plumbism, though they differed in not including intense colic but only epigastric pain and tenderness with nausea and sometimes diarrhea. The clinical picture was like that produced experimentally in animals by cadmium, involving the lungs, digestive tract, and nervous system. Eight postmortems of zinc smelters averaged in each pound of liver tissue 0.094 grain of cadmium, besides zinc and a trace of lead. Alsberg and Schwartz² experimented on cats with cadmium chlorid, CdCl_2 . It acted as a powerful emetic; the highest tolerated dose was 20 mg. ($\frac{1}{3}$ gr.) daily. Smaller doses given continuously had no cumulative effects. Small doses fed to growing rats prevented gain in weight and apparently affected the health.

Detection.—From acid, neutral or alkaline solutions either hydrogen sulphid or ammonium sulphid precipitates yellow cadmium sulphid, CdS , which is insoluble in ammonium hydroxid, carbonate, sulphid, or in dilute acids. Having excluded by their appropriate tests the other heavy metals whose sulphids are insoluble in ammonium sulphid, to detect cadmium in the presence of copper add solid potassium cyanid to the blue ammoniacal copper solution until the blue color is discharged. By passing hydrogen sulphid, cadmium alone is precipitated as yellow sulphid, CdS , whereas copper remains in solution as potassium cuprocyanid, $\text{K}_4\text{Cu}_2(\text{CN})_6$. Should copper be absent, hydrogen sulphid is passed at once through the ammoniacal solution. If a reddish or brownish precipitate falls, collect it on a filter, dry and heat on charcoal in the blowpipe flames. A brown coating denotes cadmium.

MANGANESE

(Chemical Symbol, Mn.)

Normal Manganese.—Manganese is so closely related to iron, it is not surprising that traces of it have often been detected in the blood of healthy persons. Using a new and very sensitive method, Reiman and Minot³ found that normal human blood contains from 0.005 to 0.020 mg. of manganese per 100 grams. Its wide distribution in living matter is the basis of a presumption that it is essential to life. Headden⁴ found in wheat grains amounts ranging around 40 parts per thousand of dry matter, while Jones and Bullis⁵ report appreciable amounts in the commonly grown legumes.

Symptoms.—That it was possible for manganese to be a source

¹ Jour. Indust. Hyg., 1920, 2, 129.

² U. S. Dept. Agr. Rept., 1919.

³ Jour. Biol. Chem., 1920, 42, 329.

⁴ Jour. Agr. Res., 1915, v, 349.

⁵ Jour. Ind. and Eng. Chem., 1921, xiii, 524.

of industrial poisoning was shown in the report of Embden,¹ which dealt with 4 cases with a history of a few months exposure to the dusty atmosphere of works producing manganese dioxid, MnO_2 . It gave a picture of a definite disease the main lines of which were muscular weakness, loss of whistling power, unsteady festinating gait, propulsion, and retropulsion and hand tremor in writing. All the tendon-reflexes were active. Manganese was found in the urine. Nervous affections in producers of potassium permanganate, $KMnO_4$, were proved to be due to the manganese oxid dust-laden air, when by allaying the dust the disease spread no further. In these patients von Jaksch^{2, 3} observed mental alteration shown by impulsive laughter and weeping, followed later by the symptom-complex of spastic gait, retropulsion, mask-like face, monotonous speech, and salivation. The prognosis of complete recovery was bad. The tendon-reflexes were increased. Some benefit accrued from absence from the dusty work, open-air exercise, electricity, and water cures.

Seelert⁴ in 1913 collected 15 cases of manganese poisoning reported in Europe.

In the separating mill connected with a zinc mine, the manganese and iron oxids, and silicates of the powdered ore are removed in a dry state by powerful electromagnets. The work is done in a mineral fog which leaves a thick gray dust coating on everything. Out of the many thus employed without complaint Casamajor⁵ observed 9 cases in the same mill, with a clinical history like those above described. After six months to three years service the worker was unsteady and weak in hands and feet, with a stiff and hurried gait like *paralysis agitans*. In some there was pain and stiffness in the legs or insomnia, or loss of control in writing, defective hearing, slurred speech, mask-like face, tremor of tongue and hands. The tendon-reflexes were unimpaired. The blood and urine were free from lead. After removal from the dusty magnetic room most of them improved to some extent, but the condition remained chronic though not fatal. One case dying of pneumonia showed no gross changes in brain, spinal cord, kidneys, liver or spleen. There were some indications of cerebral arteriosclerosis.^{6, 7, 8, 9}

Edsall, Wilbur, and Drinker¹⁰ reported 3 cases of workers with manganese dust that presented the same neuromuscular syndrome of a fixed type. All the records indicate that in a few persons, exposure to this dust for at least four months injures beyond repair some non-

¹ Deutsch. med. Wochenschr., 1901, xxvii, 795.

² Die Vergiftungen, 2d ed., 1910.

³ Jour. Amer. Med. Assoc., 1913, lxi, 1042.

⁴ Monatschr. f. Psych. u. Neur., 1913, 34, 82.

⁵ Jour. Amer. Med. Assoc., 1913, lx, p. 646; Dis. of Occupat. and Vocat. Hygiene, Kober and Hanson, 1916, 6, 119.

⁶ Harnack, Arch. f. exp. Path. u. Pharm., 1874-75, iii, p. 58; 1901, xlvi, p. 372.

⁷ Kobert, Ibid., 1882-83, xvi, p. 361.

⁸ Cahn, Ibid., 1884, xviii, p. 129.

⁹ Stockman, Brit. Med. Jour., 1893, i, p. 942.

¹⁰ Jour. Ind. Hyg., August, 1919, 1, 183.

vital part of the neuromuscular apparatus, but spares all other centers. The degeneration does not tend to recovery nor to spread to other parts, but in serious poisoning makes of the victim a cripple for life.¹

Pathology.—In the case autopsied by Casamajor the histologic changes showed moderate nephritis, cirrhosis of the liver, and degeneration in the fibers of the pons, none of which is considered relevant to manganese. In fact nothing is known of the pathology of this affection which helps to locate the lesion or explain the peculiar symptoms.

Absorption.—The portal of invasion of the insoluble dusts which do not irritate the skin must be either the lungs or the alimentary tract. Casamajor, in the paper cited above, gave histories of black sputum in all his cases even after the men had stopped work in the mill. Only 1 of the 9 had an intercurrent pneumonia. Whether the dust enter the blood-stream by the lungs or not, there can be no doubt that manganese oxids and silicates dissolve in the gastric juice and thereby reach the circulation.² Experiments have demonstrated that the normal blood content of manganese was increased at most twofold when dogs were fed with manganese ores. This slight rise was always temporary. Large doses given to dogs for long periods caused no pathologic symptoms nor any permanent changes in the blood and tissues.

Idiosyncrasy.—The neuromuscular syndrome, described above, as shown by a small proportion of workers in manganese industries appears to require an individual susceptibility besides prolonged exposure. Most of the workers escape any selective disease or any other marked departure from health.

Tests.—With *ammonium sulphid*, manganese in solution yields a flesh-colored precipitate which becomes brown and is soluble in acids.

With *ammonium hydroxid* there forms a white manganous hydroxid oxidizing in the air to a brownish color which dissolves pink in oxalic acid.

A small portion added to a *borax bead* and heated in the oxidizing blowpipe flame becomes first violet in color and as it cools amethystine. As a normal constituent of food, of human tissues, and excreta the detection of a minute quantity of manganese would have no significance in forensic chemistry.

VANADIUM

(Chemical Symbol, V.)

Vanadic acid, HVO_3 , is used in making dyes, by its catalytic power accelerating oxidation of anilin to anilin black. The chlorid, VCl_4 , and the trioxid, V_2O_3 , are mordants for color printing textile fabrics. A small addition of the trioxid makes a valuable alloy for the steel industries. Handling various dyes and wearing dyed clothes containing residues of vanadium chlorid, and trioxid may cause toxic effects. While all of these salts may be poisonous to those exposed to them,

¹ See Davis and Huey, Jour. Ind. Hyg., 1921, 3, 231.

² Reiman and Minot, Jour. Biol. Chem., December, 1920, 45, 135.

workers who inhale and ingest the fumes and dust of the trioxid are especially liable to the chronic intoxication vanadiumism.¹

Symptoms.—Among the most noticeable are anemia, cachexia, emaciation, irritation of eyes, nose, and throat, dry paroxysmal cough with occasional hemoptysis.

The digestive apparatus is disturbed by anorexia, nausea, diarrhea alternating with constipation. Kidney involvement is denoted by urinary albuminuria, tube-casts, and blood. Later on appear nervous phenomena, such as headache, vertigo, melancholia, fine tremors, retinitis, and amaurosis. It may even have a fatal termination when complicated with other diseases.

Postmortem Appearances.—The mucosa of stomach and intestines show degrees of inflammation, the lungs are congested, and the alveolar epithelium degenerated. The kidneys give evidence of nephritis, sometimes hemorrhagic.

Elimination is by the urine and feces, it can often be detected in the saliva.

Prevention is to be aimed at by free ventilation and all other measures to lower the hazard from fumes and dust in the air. This may include light plugs of cotton in nostrils and ears, a respirator, a thin ointment spread over the face and neck, a daily shower bath, and changes of clothing.

Treatment.—This would include absence from the works, open-air life, tonics, and eliminants beside other symptomatic remedies.

Detection.—Vanadium solution is precipitated when ammonium sulphid is added and then a slight excess of hydrochloric acid. The sulphid is brown and soluble in ammonium sulphid.

Bead Test.—Heated with borax in the outer oxidation blowpipe flame a small quantity of a vanadium salt yields a clear colorless bead; a large quantity, a bead yellow while hot, colorless when cold, and which turns green in the inner reduction flame.

The only acids red in solution are vanadic and chromic; when de-oxidized the former turns blue, the latter green.

Vanadic acid or an acidulated solution of a vanadate when shaken with ether and hydrogen dioxid leaves the ether colorless, while the aqueous solution turns red. This reaction is sensitive when the vanadic acid is present 1 part in 40,000 of liquid.

METALS OF THE ALKALINE EARTHS

BARIUM

(Chemical Symbol, Ba.)

Certain salts of barium used in pyrotechny, in wood-staining, and in glass-making sometimes figure in toxicology as irritant poisons which, when absorbed, cause cardiac depression and convulsions. Vinegar, made from dried apple products which have been sulphured, is often treated with barium carbonate to remove sulphur compounds and hence

¹ Dutton, Jour. Amer. Med. Assoc., 1911, lvi, 1648.

may contain soluble barium salts. Common salt (NaCl) has been found to contain ponderable amounts of barium chlorid as a not infrequent impurity, so that the U. S. Bureau of Chemistry has established as a standard of purity the presence of not more than 0.05 per cent. of barium chlorid in common salt.¹ The *chlorid* and the *nitrate* occur in white, soluble crystals resembling the ordinary purgative "salts," for which they have been taken by mistake.

Barium carbonate (BaCO_3) occurs native as "witherite," a white crystal slightly soluble in water and freely so in acids. When powdered and mixed with arsenic trioxid it is an active part of the vermin killer "Rough on Rats" (p. 243). Crawford^{2, 3} expressed the opinion that the barium compounds that are sometimes found in the "loco-weed" were the cause of loco-poisoning of live stock in the grazing lands of the western states. On the other hand, Alsberg and Black^{4, 5} made a careful investigation and concluded that barium was not responsible for this disease.

Barium Sulphate (BaSO_4).—Heavy spar is called "permanent white" when used as a water-color pigment. It is a heavy white crystal, insoluble in water and acids. It has supplanted bismuth carbonate for the contrast-meal in Roentgen-ray work as it is cheap, opaque, and harmless. Only the chemically pure article should be used. Fatalities have occurred owing to the blunders of pharmacists, who instead of the sulphate have dispensed the carbonate, the sulphid, or the chlorid, all of which are soluble in the stomach and rapidly fatal. Two such mishaps were reported in Prague,⁶ each taking 50 grams of the carbonate in suspension in water for Roentgen work. The first woman collapsed in a few minutes, had violent cramps, loss of consciousness, paralysis of respiration, and died in the office. The second, younger, suffered less and survived long enough to be taken to a hospital. Two fatal cases were described by Bensaude and Antoine.⁷ One, a robust woman of twenty-seven, died ten minutes after taking a suspension of 40 grams of barium polysulphid mistaken for the sulphate. A man of thirty-seven took 80 grams of barium carbonate, vomiting part of it in the third hour. Sodium sulphate and magnesium sulphate were given as antidotes and thus death was delayed until the thirty-fifth hour.

Barium Sulphid (BaS).—In a review of the literature for seventy-five years Steden⁸ collected only 4 cases of poisoning by this salt. It had been given by mistake for barium sulphate, in doses of 2 to 4

¹ See Service and Regulatory Announcement No. 13, Bureau of Chemistry, U. S. Department of Agriculture.

² Jour. Amer. Med. Assoc., 1908, 1, 458.

³ Ibid., 1908, li, 1338.

⁴ Bull. 246, U. S. Dept. Agric. Plant Indust., 1912.

⁵ Jour. Amer. Med. Assoc., 1912, lix, 2258.

⁶ Vienna letter, Jour. Amer. Med. Assoc., 1912, 58, 2041. See also Krause, Deutsch. med. Wchnschr., 1912, 48, 319.

⁷ Bull. Soc. med. des Hôp., Paris, 1919, 43, 15; see also Mayrhofer and Meixner, Wien. klin. Woch., 1919, 32, 1068; Krafft, Ztschr. f. Nahr. u. Genussm., 1921, 42, 390.

⁸ Bull. Pharm., 1920, 34, 40.

ounces (62–124 gm.). In his experiments he administered $\frac{1}{4}$ grain (0.015 gm.) on four successive days to a guinea-pig weighing 8 ounces (248 gm.) with no apparent injury. He himself while fasting took 61 grains (3.95 gm.) and felt no evil after-effects.

Symptoms.—Gastro-intestinal irritation is shown by vomiting and diarrhea, with straining and abdominal pain. After absorption dilatation of the pupils with convulsions, paralysis, and heart failure may supervene.¹

Fatal Dose.—About 100 grains (6.5 gm.) of the chlorid proved fatal to a woman, although, by gradually increasing the daily quantity, Pivondi was enabled to take in divided doses 119 grains (7.7 gm.) in one day.

Fatal Period.—Death occurred in 1 case in ten minutes, in another in one hour, in another in fifteen hours, in another in thirty-four hours, and again as late as a week after taking the poison.

Treatment.—The best chemical antidote is magnesium sulphate (Epsom salts) or sodium sulphate (Glauber's salts). Both have the power to precipitate the barium as insoluble sulphate. The stomach should then be washed out with milk and water. Anodynes are indicated for the pain; heat and stimulants for the cardiac depression.

Postmortem Appearances.—Any or all of the signs of gastro-intestinal inflammation may be present—*i. e.*, patches of redness, swelling, softening, effusions, ulceration, and even perforation.

Linossier,² by experiments on rabbits, found that after chronic poisoning for thirty days all the organs contained barium—the bones most of all, the kidneys, brain, and spinal cord showed a less amount, the liver still less, and traces only were in the lungs, heart, and muscles.

Tests.—1. *Dilute sulphuric acid* precipitates barium sulphate, which is insoluble in hydrochloric or nitric acid.

2. *Neutral potassium chromate* gives a yellow precipitate, insoluble in water, but soluble in nitric or hydrochloric acid.

3. A green hue is given to a colorless flame when a barium salt is held in it by a loop of platinum wire moistened with hydrochloric acid.

Detection.—Having dissolved the organic matter by hydrochloric acid and potassium chlorate and precipitated most of the common metals by hydrogen sulphid and ammonium sulphid, remembering that a portion of the barium may be present as insoluble barium sulphate in the initial residue left after treatment of the tissue with hydrochloric acid and potassium chlorate, the filtrate may be tested for soluble barium salts by dilute sulphuric acid. The initial residue spoken of above as containing barium sulphate may be incinerated, fused with sodium carbonate, the metal taken up with water and filtered, the insoluble barium compound (barium carbonate) now being dissolved in dilute hydrochloric acid and tested with dilute sulphuric acid.

Instead of the above method, the organic matter of the tissues may be burned in a crucible placed in an electric muffle where there

¹ See Salant and Kleitman, Jour. Pharm. and Exp. Therap., 1922, 20, 247.

² London Med. Record, 1887, 15, 471.

is little chance of volatilization of the barium, or the tissue may be treated with nitric and sulphuric acids (as in the method of Gautier), the liquefied material evaporated until white fumes of sulphuric acid are evolved (in order to drive off any hydrochloric acid that may be present), and this residue transferred to a platinum dish and incinerated. In either case fuse the ash with sodium carbonate, take up the melt with water, filter, dissolve the residue on the filter with dilute hydrochloric acid, and test this solution for barium by the addition of dilute sulphuric acid.

MAGNESIUM SULPHATE

As a cathartic alone or as an ingredient of Glauber's salt or of various natural purgative waters, magnesium sulphate is frequently administered. For this purpose it is best given dissolved in a large amount of water. The local irritant action excites peristalsis while the unabsorbed liquid softens the fecal mass. Epsom salts has been taken by mistake for sugar in solid crystals; it has been taken ignorantly in concentrated solution repeating the dose because of failure to act. It is to be remembered that magnesium sulphate, as oftentimes marketed, may contain sufficient arsenic as an impurity to cause toxic and even fatal results. The dry salt slowly dissolves in the alimentary fluids and, not acting as a purge, inflames the mucosa and is absorbed. After circulating in the blood-stream, it is eliminated slowly in great part by the kidneys, though anuria may occur for a time. If there be no mechanical obstruction, the rapid onward movement of the purgative, when it is diluted, prevents absorption. If this movement is obstructed or is delayed by sluggish peristalsis, the salt is absorbed even from dilute solution. In any event, if a sufficient amount of the salt be absorbed, general intoxication follows. Sometimes the failure to purge leads to repeated doses in concentrated solution at short intervals. This favors absorption and accumulation in the circulation and, eventually, leads to paralysis of the bowels. Menig¹ has found the toxic action of magnesium sulphate so marked that he employs an injection of a concentrated solution into the peritoneal cavity as a rapid means of killing animals.

Symptoms.—The intravenous injection of magnesium sulphate by Meltzer and Auer² induced general anesthesia and relaxation of the abdominal walls. Repeated doses paralyzed the skeletal muscles and the reflexes and abolished respiration. The margin of safety was too small for a general anesthetic, one of the earliest effects being, in some cases, respiratory paralysis.

It has been used to control the convulsions of tetanus and as a local anesthetic by subcutaneous injection.³ In a study of 2 cases reported by himself, and 8 by others, Boos⁴ noted that 6 were fatal; in only 1 was there active purging and in 5 there was no purging whatever. The paralysis of the bowel with enteritis called for laparotomy

¹ Personal communication.

² Amer. Med., 1905, x, 916; Med. Record, 1905, lxxviii, 965; Amer. Jour. Physiol., 1905-06, xiv, 366; Jour. Exper. Med., 1916, xxiii, 641.

³ Mendel and Benedict, Amer. Jour. Physiol., 1909-10, xxv, 1.

⁴ Jour. Amer. Med. Assoc., 1910, lv, 2037.

in 2 cases. Vomiting occurred in 5. The urine was scanty in all and in some was suppressed. There was paralysis of the respiratory and motor nerves, and of the reflexes; 2 had convulsions.

Curtis¹ employed hypodermoclysis of magnesium sulphate, following the method of Gwathmey,² using 310 c.c. of a 4 per cent. solution of chemically pure magnesium sulphate as an aid to the nitrous oxide-oxygen anesthesia. Death occurred sixty hours after operation, following a period of marked prostration. Postmortem examination showed intense jaundice, extensive acute fatty changes in the liver, marked cloudy swelling of the parenchymatous organs, multiple petechial hemorrhages of the pleura, pericardium, and endocardium. The lining of the stomach and bowels was unchanged. Chemical analysis of the liver showed a magnesium sulphate content of 5.33 grams, after deducting the amount normally present in the human liver.

Treatment.—A case reported by Fraser³ illustrates the remedial value of normal saline solution infused subcutaneously at a critical stage. A boy, three and a half years old; mistaking Epsom salts for sugar took $1\frac{1}{2}$ ounces and washed out the bitter taste with milk. In a few minutes he had gastric pain, thirst, and vomiting. Twenty-five hours later he was almost in collapse, the urine was very scanty, and the bowels were unmovable. The temperature was 100° F., pulse small with a rate of 160, respiration labored, thirst intense. The abdomen was distended, rigid, and hyperesthetic as in peritonitis, so that a laparotomy was performed but no mechanical obstruction to the bowels was found. For forty-eight hours he was moribund. Subcutaneous saline injection was given in the axilla, and $\frac{1}{2}$ grain of calomel was administered every hour. Improvement set in, the bowels were opened, and a good recovery ensued quickly. The saline infusion, diluting the Epsom salt in the circulation, lessened its toxicity and promoted its excretion by the kidneys.

THORIUM

(Chemical Symbol, Th.)

This is a radio-active metal of the tin group. **Thorium nitrate**, $\text{Th}(\text{NO}_3)_4 \cdot 6\text{H}_2\text{O}$, is a freely soluble salt extensively used for incandescent gas mantles. It has been suggested as possibly a good contrast-medium in Roentgen work. In the light of recent experience this is a dangerous error. Francois⁴ reported an irritant effect on the bladder, following an injection into that organ of a solution of that salt to serve as an opaque medium for the Roentgen ray. He was compelled to perform an emergency cystotomy as the patient was unable to evacuate the bladder and catheterization was impossible. A fatality due to acute toxemia was studied at the Mayo Clinic by Weld.⁵ A woman,

¹ Jour. Amer. Med. Assoc., 1921, lxxvii, 1492. See also Greenough, *Ibid.*, 1922, lxxviii, 1148.

² *Ibid.*, 421.

³ Lancet, 1909, i, 1174; see also report of 2 cases by Anderson, Georgia Med. Assoc. Jour., 1921, 10, 826.

⁴ Belgian letter, Jour. Amer. Med. Assoc., 1921, lxxvi, 880.

⁵ Jour. Urology, October, 1919, 2, 415.

aged fifty-five, under diagnostic examination had thorium nitrate as a pyelographic medium carefully introduced by catheterization, to the pelvis of the kidney. There was no immediate pain but some faintness for a time, yet the patient was able to return to the hotel. At the end of six hours, she was suddenly seized with nausea, vertigo, and weakness. She grew rapidly worse with marked vomiting and prostration, dying nine hours after the pyelogram. The autopsy revealed general arterial sclerosis, some atrophy of the kidney, edema of the lungs, and fatty changes in the liver.

Physiologic tests were then made on dogs with 15 per cent. solutions of thorium nitrate given intravenously. One of the marked toxic effects was on the heart muscle direct, causing a rise of blood-pressure and in 4 out of 6 cases followed by fatal heart failure. This ending occurred in spite of elimination of the central nervous system by section of the vagi; of the nerve ganglion by doses of nicotin; of the nerve endings by doses of atropin. Toxicity varied with the different ages of the five different solutions due possibly to the conditions under which they were kept.

All pyelographic media and various dyes are rapidly absorbed from the pelvis of the kidney and produce their systemic effects.

GASEOUS POISONS

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THE inspired air contains 20.96 vol. per cent. of oxygen, nitrogen and argon 79. per cent., carbon dioxid 0.04 per cent., with minute traces of hydrogen, xenon, krypton, neon, variable amounts of ammonia, ozone, in addition to floating dust particles and micro-organisms. The expired air contains oxygen 16.4 vol. per cent., nitrogen 79.5 per cent., carbon dioxid 4.10 per cent. These figures for the composition of inspired and expired air refer to dry air at a temperature of 0° C. and 760 mm. Under normal circumstances inspired air contains a variable amount of aqueous vapor and has a variable temperature corresponding with the time of the year. When awake a man takes in 350 c.c. of oxygen, and gives out 300 c.c. of carbon dioxid per kilo per hour. With the tidal air of 500 c.c. respiratory rate of 17, the total pulmonary ventilation during the hour would be $500 \times 17 \times 60 = 510,000$ c.c. per hour.¹

Oxygen alone supports human life; the inhalation of any other gas is followed by suffocation—that is, by suspended animation due to obstruction of blood aëration. According to Hill² the changes in the chemical composition of the atmosphere have no relationship whatsoever to the unhealthful influence of vitiated air. Seven healthy young men were allowed to remain in an air-tight cabinet, provided with an electric fan and with the necessary apparatus for measurements of the physical and chemical conditions of the air. "No ventilation was allowed after forty-four minutes; the dry bulb stood at 87° F., the wet bulb at 83° F. The carbon dioxid had increased to 5.26 per cent., the oxygen had fallen to 15.1 per cent. The discomfort felt was great, all were wet with perspiration and the skin of all flushed. The talking of the occupants had gradually become less and then ceased; on putting on the electric fans and the whirling of the air, the relief was immediate. No headaches or after-effects have followed this type of experiment, which has been repeated five times." The temperature and humidity are more important than the carbon dioxid content.³ From Winslow's experiments in rebreathed stale air, containing 20 parts of carbon dioxid, no discomfort was noted if the temperature was not allowed to rise. In a second experiment he found warm stale air, or fresh air if warmed, produced distinct and clearly marked physi-

¹ Starling, *Principles of Human Physiology*, 1915, 1052.

² Hill, Rowlands, Walker, *Jour. Physiol.*, 1910, xli, 3.

³ Winslow, C. E. A., *Amer. Jour. Pub. Health*, 1917, 7, 827.

ologic reactions. At a temperature of 75° F. with 50 per cent. relative humidity the rectal temperature was 2° C. higher and at 86° F. with 80 per cent. humidity was 0.5° C. higher with the pulse increased 5 to 12 beats.

Gases differ widely in their mode of action. Some, like nitrogen, merely exclude the oxygen of the air from the lungs, and the blood is then gradually exhausted of its oxygen. Life is restored in such cases when efforts to produce artificial respiration are not too long delayed and are sufficiently protracted. It may take an hour or more of persistent effort to revive a patient, and the rules laid down for the resuscitation of the drowned are applicable. Other gases, such as carbon monoxid, deprive the blood of its property of absorbing oxygen. They act directly upon the blood-corpuscles and are specific poisons. Such gases greatly retard or even prevent reoxygenation. Still other gases, like hydrogen sulphid, entering the system by absorption through the air-cells of the lungs, pass rapidly into the circulation and produce effects on special organs or on parts of the nervous system.

The only gases supposed to be purely negative in their action are nitrogen and hydrogen. To these the recently discovered argon may be added. There are no direct experiments on its inhalation. It is present in the air to the extent of nearly 1 per cent. without producing ill effects. Truly poisonous gases, even though present in much smaller quantity than this, seriously affect the organism. We are thus led to the assumption that argon is as passive in this as in all other respects. Since hydrogen when breathed with oxygen in atmospheric proportion has been found to produce narcotism, it should not, perhaps, be classed with nitrogen.¹

Experiments made on rats confined in a space in which they could live in air without inconvenience for three hours showed the relative periods in which certain gases proved fatal.² Thus pure nitrous oxid killed in twenty-five seconds; pure hydrogen, in nine minutes; pure carbon dioxid, in eight seconds. Since experiments conducted by the Committee of the Medico-Chirurgical Society showed that the heart's action continued for eight minutes and twenty seconds under a complete deprivation of air, the above results indicate the truly poisonous action of vapors and gases, a conclusion substantiated by other facts.³

Although a large number of gases are poisonous, and although very many of them have at times produced death or serious effects, only the most important will be considered in detail in this section.

The following references to certain physical and chemical properties of the atmosphere have a bearing on the forensic as well as the hygienic side of this section:

Effect of Pressure on Respiration.

Bert, *Compt. Rend.*, 1872, lxxiv, 617; lxxv, 29, 88, 491, 543.

Hoppe-Seyler, *Physiologische Chemie*, 1877, p. 7.

¹ Taylor, *Medical Jurisprudence*, 11th Amer. ed., 1892, p. 439.

² Norris, *Brit. Med. Jour.*, 1873, ii, 401.

³ Taylor, *Medical Jurisprudence*, 11th Amer. ed., 1892, p. 493.

Effects of Ozone.

Hoppe-Seyler, *Physiologische Chemie*, p. 398.

Kobert, *Lehrbuch der Intoxikationen*, Stuttgart, 2d ed., 1906, ii, 45 and 775.

Removal of Oxygen by Plants.

Phipson, *Analysis of the Air by a Mushroom*, Chem. News, 1896, lxxiv, 247.

Impurities in the Air.

C. F. Mabery, *An Examination of the Air of a Large Manufacturing City*, Jour. Amer. Chem. Soc., 1895, xvii, 105.

Parkes, *A Manual of Practical Hygiene*, New York, 1884.

Woodman and Tidy, *Forensic Medicine and Toxicology*, Philadelphia, 1877, 856.

Newth, *Inorganic Chemistry*, London, 1898, 227.

J. Th. Hermanns, *Ueber die vermeintliche Ausathmung gasfoermiger organischer Substanzen durch den Menschen*, Arch. f. Hygiene, 1893, i, 5.

Parkes, op. cit., 142 and 161.

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Annual Register, 1858, p. 278; letter of J. Z. Holwell, Esq., Black Hole of Calcutta.

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Wagenaar, *Analysis of Air from Submarines* (see under Arsine), Wilemsodt Pharm. Weekblad 1919, 56, 1001.

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Palmer, G. T., *New Sampling Apparatus for Aërial Dust*, Amer. Jour. Pub. Health 1916, 6, 54.

Bill, J. P., *The Electrical Method of Dust Collection as Applied to Sanitary Analysis of Air*, Jour. Indust. Hyg., 1919, 11, 323.

Henderson, G., and Haggard, H. W., *The Physiological Principles Governing Ventilation when the Air is Contaminated with Carbon Monoxid*, Jour. Ind. and Eng. Chem., 1922, 14, 229.

Legge, T. M., *Industrial Poisoning in the Manufacture of Airplanes, Explosives, and Dyes*, Jour. Ind. Hyg., 1920, 121.

Winslow, C. E. A., *A Study of the Dust Hazard in the Wet and Dry Grinding Shops of an Ax Factory*, Health Reports, 1920, vol. 35, No. 41, October 8th.

Studies of Air Pollution of City of Chicago, Article 21, April 1 to August 30, 1912, Smoke Papers, Chicago Association of Commerce.

CARBON DIOXID¹

(Chemical formula, CO₂ = 44; Synonyms: *Fixed Air*; *Choke Damp*; *Carbonic Acid*; *Carbonic Anhydrid*)

Carbon dioxid is one of the commonest of all gases, being abundantly produced by a large number of natural and artificial processes, such as respiration, decay, alcoholic fermentation, combustion of coal and wood, lime-burning, etc. It is a heavy gas, having a specific gravity of 1.52 compared with air, and on account of its weight is rather slowly diffusible.² For these reasons it not infrequently is found in caves, old wells and cisterns, and other low and confined places, and has often been the cause of death of persons entering them.³ Hayhurst and Scott⁴

¹ Consult also p. 392 in section on Death from Asphyxia.

² Wharton and Stille, *Medical Jurisprudence*, 1884, ii, 546.

³ Briand and Chaudé, *Manuel Complet de Medecine Legale*, 6me ed., 1858 and 18me ed.

⁴ Hayhurst and Scott, *Ohio State Board of Health Bulletin*, 1914, iv, 1407.

report 4 deaths of men engaged in tramping down silage at a depth of about 6 feet from the top of the silo. An analysis of the air in the silo gave carbon dioxide 38 per cent., oxygen 13.5 per cent., nitrogen 48.5 per cent. Although it is only slightly diffusible, no separation of the gases subsequently takes place when once the carbon dioxide is thoroughly mixed throughout the air.¹

Action on Body.—Carbon dioxide acts *locally* on the point of application, or *remotely* on the brain and spinal cord. Applied to the skin it produces a prickling or twitching, together with a feeling of warmth which, if the stream is continued, is followed by anesthesia. In olden times local anesthesia was brought about by rubbing the skin at the place to be operated on with vinegar and powdered marble.² More profound symptoms arise when larger surfaces are affected, and bathing in water charged with CO₂ causes a diminution of sensitiveness, reddening of the skin, warmth, prickling, and lowering of pulse-rate.

The gas disappears rapidly when injected subcutaneously without serious symptoms arising (Bernard). Others ascribe serious symptoms to the gas swallowed in aerated waters.³

Carbon dioxide renders arterial blood venous more rapidly than other gases. It acts on diluted blood as other weak acids. The hemoglobin is converted into acid hematin. A slight increase in the number of erythrocytes was noted in rabbits exposed to 4 per cent. carbon dioxide for four days.⁴ A solution of oxyhemoglobin treated with CO₂ yields a two-banded spectrum. On the evacuation of the carbon dioxide, the solution not coming in contact with the air, reduced hemoglobin is produced.⁵ Muscular tissue loses irritability and becomes rigid in gaseous mixtures containing much carbon dioxide. Ciliary movements are also arrested.

The brain and spinal cord are first stimulated, causing increase of blood-pressure,⁶ peristaltic movement, and reduction in pulse-rate, followed by more intense respiration and less psychic excitability, and finally paralysis. Absorption takes place through all mucous membranes, the lungs, subcutaneous tissues, and also by the skin. Carbonates are changed to bi- or acid-carbonates in the blood or tissues.

The elimination is quantitative, and occurs by the lungs, urine, skin secretions, and intestinal discharges.

Death is ascribed in CO₂ poisoning, sufficient oxygen being supplied, to an excessive stimulation of the cerebrospinal system producing asphyxia, differing, however, from ordinary asphyxia, in which a loss of stimulation, especially of the heart, is due to the want of oxygen.⁷

Symptoms.—These are either sudden or gradual, according to the degree of concentration of the gas breathed. Inhalation of the pure

¹ See Jour. Amer. Med. Assoc., 1921, 77, 711.

² Demarquay, Compt. Rendus, 1865, lxi, 166.

³ L. Hermann, Lehrbuch der exp. Toxikologie, Berlin, 1874, p. 115.

⁴ Dufton, Proc. Physiol. Soc., London, 1917, 51, 5.

⁵ Buckmaster, Proc. Physiol. Soc., London, 1917, 51, 105.

⁶ Cathcart, Jour. Physiol., 1915, xlix, 301; S. Itami, Jour. Physiol., 1912, xlv, 338.

⁷ R. Kobert, Lehrbuch der Intoxikationen, Stuttgart, 2d ed., 1906, ii, 1121;

L. Hermann, Lehrbuch der exp. Toxikologie, Berlin, 1874, p. 121.

gas is followed by a spasm of the glottis, insensibility, and death from apnea unless the patient is speedily removed to a pure atmosphere. When the amount of CO_2 is smaller, there is a tendency toward giddiness, somnolence, and loss of muscular power. Profuse perspiration and nausea are common. If oxygen deficiency is excluded by inhaling gas mixtures containing 20 per cent. oxygen, no effects occur until the concentration is 3 per cent. (Zuntz), when there is hyperpnea and discomfort; $8\frac{1}{2}$ per cent. produces in man in a few minutes distinct dyspnea, rise of blood-pressure and congestion which become unsupportable in twenty minutes, but disappear promptly in fresh air. The symptoms increase to 15 per cent., but are not dangerous to animals in an hour and probably not to man. With 25 to 30 per cent. the stimulant phenomena pass into depression, with diminished respiration, fall of blood-pressure, coma, generally without convulsions. The sudden loss of muscular power on entering a poisonous atmosphere is illustrated in the unfortunate accidents that are the most frequent cause of death by this poison. A workman enters a vat or other receptacle to clean it; a well, to dig it deeper, and is overcome. Another going to his rescue sacrifices his life, becoming powerless in the tainted air.

When the gas is in fatal proportion, there is a sensation of great weight in the head, of pressure in the temples, of singing in the ears, of a pungent sensation in the nose (similar to that given by drinking gaseous beverages), of giddiness, and of a loss of muscular power, and there is a strong desire to sleep.

If erect, the person falls to the ground as if struck; the body collapses, the head falling on the breast. The breathing, at first stertorous, becomes suspended. Convulsions may supervene, but not when a sufficiency of oxygen is present. The action of the heart, at first violent, ceases; sensibility is lost and coma follows. The body remains warm, the limbs flaccid, although occasionally rigid or convulsed. The countenance assumes a livid color (unless carbon monoxid is likewise present), especially noticeable about the eyelids, lips, and throat. Sometimes, however, the face is pale and the features are placid. Death generally occurs without a struggle. Those resuscitated have complained of pain in the head or soreness of body lasting some days. Paralysis of the facial muscles has ensued. Persons may become gradually accustomed to the gas and continue to breathe an atmosphere that to any one entering would be unbearable.

Treatment.—Removal of the body as speedily as possible to fresh air, and inhalation if possible, of oxygen; cold affusions, galvanism, artificial respiration, friction, and venesection are resorted to if necessary. That resuscitation may take place after long insensibility has been shown by experiments on animals and experience with human beings. Doremus has observed pulsations of the heart in animals whose chests were opened after being many minutes in a concentrated atmosphere of carbon dioxid, and when general lividity of the body indicated a deep-seated poisoning. The same animals serve over and

over again for the demonstration of the poisonous effect of the air of the Grotto del Cane near Naples.

Postmortem appearances are those of death from asphyxia. Sometimes the face is livid and swollen and the features distorted, but not infrequently they are pale and placid; the position of the body indicates that the person has died without a struggle. The venous system and right heart are found filled with a dark-colored liquid blood, while the vessels of the lungs and brain are congested. There is nothing very characteristic in the general appearance, and death may be ascribed to apoplexy or to some other cause. Carbon dioxid, being a narcotic poison, induces cerebral congestion and apoplexy.

Tests.¹—The air of a room contains too much carbon dioxid if a measured ounce of lime water becomes turbid when shaken in a half-pint bottle of the air. This would be about 0.1 per cent. When the quantity reaches 0.5 per cent., most persons are attacked with languor and headache; while when the air contains the twelfth of its volume, suffocation is caused. The ordinary test of such confined air is the indication of the candle-flame, when any dimming of the same should warn against a person entering the space. The taper is extinguished when the proportion is above 12 or 15 per cent. Barium hydroxid is a better test than calcium hydroxid (lime water). The air is shaken with or drawn through a quantity of this solution of known strength, and the loss of alkalinity determined by titration with dilute acid. Fifty cubic centimeters of barium hydroxid solution are added to a bottle of 5 or 6 liters capacity, which has been filled with the air of the room by the use of a flexible bellows pump. After thoroughly shaking the liquid with the air and after the lapse of half an hour, the turbid liquid is transferred to a stoppered separating funnel, the stem of which passes through a rubber stopper fitted to the neck of a bell-jar. One end of a piece of narrow flexible metallic tubing is inserted in the second perforation in the stopper, and the other end of the tube fits a small cork which closes the top of the tap-funnel. The bell-jar contains a small beaker, above which rests a funnel provided with an asbestos plug, previously washed with baryta water. The bell-jar also contains sticks of moist potassium hydroxid to free the air of the jar of carbon dioxid. The barium hydroxid liquid is thus filtered in an atmosphere free of carbon dioxid. An aliquot portion of the filtered liquid is titrated with nitric or hydrochloric acid, phenolphthalein being used to indicate the point of neutralization.² When the amount of carbon dioxid is large, its quantity may be determined by observation with a eudiometer with the aid of potassium hydroxid solution. The dried air may also be drawn through a weighed vessel containing potassium hydroxid solution, when an increase in weight will show the amount of carbon dioxid in the volume of air submitted to analysis.

¹ See Van Slyke and Cullen, Direct Method of Carbon Dioxid Capacity of the Plasma, *Jour. Biol. Chem.*, 1917, 30, 289; *Jour. Biol. Chem.*, 1917, 30, 347.

² Williams, Commemoration Volume, University College, Sheffield, 1897, p. 132.

When the air of a well, vat, or similar receptacle is to be tested, a sample for examination may be obtained by lowering into it a bottle containing fine sand and inverting by means of a cord attached to the bottom; when the sand running out is replaced by the air, the bottle is raised, mouth up. Using the Petterssen-Palmquist method the carbon dioxid can be determined in air in a 25 c.c. sample with an accuracy of 1 part in 10,000 and there is no necessity of making corrections for variations in pressure and temperature. This is accomplished by using a compensating tube filled with air and in communication with one side of a manometer tube; the buret containing the air to be measured is attached to the other side of the manometer tube; the compensating tube and buret are of nearly the same capacity and are in water. If the temperature of the water around the tubes changes during the experiment, the effect on the volume of air in each tube is the same. The carbon dioxid is absorbed in an Orsat gas pipet containing a solution of potassium hydroxid.¹

CARBON MONOXID

(Synonym, *Carbonic Oxid*)

Carbon monoxid when pure is nearly insoluble in water, colorless, tasteless, and a practically odorless gas, this latter physical property making it especially dangerous as a source of poison. It combines with metals such as nickel and iron to form colorless liquids called carbonyls. Heat decomposes these with deposition of the metal and evolution of the gas. Combination of carbon monoxid with ehlorin forms carbonyl chlorid (phosgene) which was used as a toxic war gas and has also caused industrial poisonings.² It does not support combustion, but forms an explosive mixture with one-half its volume of oxygen, or two and one-half volumes of air. It is highly poisonous. By maintaining a pressure of 200 to 300 atmospheres at -136° and then reducing the pressure to 50 atmospheres the gas becomes a colorless transparent liquid.³ Carbon monoxid has the formula CO and its molecular weight is 28.

Carbon burns directly to carbon monoxid at 1000° C.⁴ It is produced at the electrodes or from the charges of electric furnaces. It is also produced in blast furnaces. In electric furnaces having limestone linings the carbon dioxid is reduced to carbon monoxid at the heated electrodes,⁵ the gas escapes unburned, producing characteristic symptoms. The most common sources of carbon monoxid, with exception of its marked formation during a severe lightning storm,⁶ are coal

¹ Dennis, L. M., *Gas Analysis*, 1913, 382; Tashiria, *A Method of Detecting Small Amounts of Carbon Dioxid*, *Proc. Soc. Biolog. Chem.*, 1912, 14, 41.

² See Wiki, *Rev. Med. de la Suisse Rom.*, 1921, xli, 38; Hermann, *Virchow's Arch. f. path. Anat.*, 1921, cexxxi, 480; Baskerville and Cohen, *Jour. Ind. and Eng. Chem.*, 1921, xiii, 333.

³ Wroblewski and Olszewski, *Amer. Chem. Jour.*, 1884, 6, 1128.

⁴ Bloxam's *Inorganic and Organic Chemistry*, 8th ed., 1895, 95.

⁵ Moissan, *Le Four Electrique*, Paris, 1897, 150.

⁶ W. M., *Science*, 1920, n. s., li, 437.

stoves, grates, salamanders, domestic, and industrial furnaces,¹ gas engines,² fumes from explosions, smoldering ashes,³ and mine, coal, natural, and artificial gases. It is formed whenever incomplete combustion of carbon occurs, such as flames on besotted surfaces and low burning oil lamps.⁴ Tobacco smoke⁵ contains 80 c.c. of carbon monoxid to each gram of tobacco burned.⁶ From Bunsen burners⁷ the percentage of carbon monoxid varies from 0.04 to 0.51 per cent. according to the air mixture. While carbon monoxid may accumulate rapidly from any of these sources, the natural sources of disposal are such that danger arises only when the supply of oxygenated air is depleted.⁸

The blue flame at the surface of the fire in grates and blast furnaces shows the presence of carbon monoxid. Much escapes unburned. In furnaces with forced draft the blue flame is often seen at the top of the chimney, and in iron blast furnaces the gas is conducted and burned in the superheaters of the air supply. It is, therefore, a constant constituent of the products of combustion of carbonaceous materials,⁹ and while the poisonous action of charcoal, coke, or coal vapors is in part due to carbon dioxid, it is mainly due to this more poisonous gas. Quantities of this accumulate above the fire in hot-air furnaces and stoves. So much, indeed, that on opening the door the inrush of air will form an explosive mixture that, igniting, may produce serious accidents. The common construction of dampers is that they shall be loose enough to allow a constant draft to the chimney. Notwithstanding this, it frequently happens that a down draft fills the room with the products of combustion to a poisonous extent. A large proportion of the accidents that happen yearly is due to the leaving off of the stove-lids.

¹ Willcox, Asphyxiation from Blast Furnace Gas, Technical Paper 106, Dept. of the Interior, Bureau of Mines, Washington, D. C., 1916.

² Hood and Kudlich, Bulletin 74, Dept. of the Interior, Bureau of Mines, Washington, D. C., 1916; Carbon Monoxid Poisoning in Closed Garages, Pub. Health Rep., 1921, 36, 2215. Harbitz, F., Poisoning from Exhaust Gases in Motor Boats. Norsk Magazine for Laegevidenskaben, Christiania, 1917, 78, 462, or Jour. Amer. Assoc. 1917, 69, 1746. Burrell G. A., and Gauger, Vitiating of Garage Air by Automobile Gases, Technical Paper 216, Dept. of the Interior Bureau of Mines, 1919, Washington, D. C.

³ Albaugh, Ohio Public Health Jour., 1917.

⁴ Langden, S. C., Jour. Amer. Chem. Soc., 1917, 39, 149. reports the presence of carbon monoxid in the gases evolved from growing kelp.

⁵ Thompson, Lancet, London, 1904, 1, 395; Fleig, Compt. rend. Acad. d. sc., 1908, 146, 1776.

⁶ Using an intermittent aspirator to imitate the smoking of tobacco, one of the writers (McNally) found that the carbon monoxid from the inhaled smoke from cigarettes was from 0.014 to 0.26 per cent. of the tobacco and paper consumed, from cigars, it was from 0.027 to 0.15 per cent., and from pipe tobacco 0.027 per cent.

⁷ Terres, Jahrb. fur Gasbeleuchtung, 1914, 57, 605. See Kling, A., and Florentin, D., Production of Carbon Monoxid in Flames from Incandescent Burners, Chemie et Industrie, 1921, 6, 305. Brumbaugh and Jones, G. W., Hazards of Carbon Monoxid from Gas Burners, Gas Age Record, 1922, 49, 427.

⁸ See Lamb, Bray, and Frazer, The Removal of Carbon Monoxid from the Air, Jour. Ind. and Eng. Chem., 1920, xii, 213.

⁹ See chapters on Death from Asphyxia, p. 407, and on Industrial Toxicology, p. 791.

It was thought at one time that carbon monoxid passed through heated iron. An important investigation was reported to the French Academy. Subsequent investigation, however, has indicated that such transpiration does not take place. The presence of any carbon monoxid in the atmosphere is due either to the faulty construction of the furnace, or to the action of the heated plates on the organic dust with which they are generally covered.¹ Notwithstanding all attempts to render furnaces gas-tight, their lack of this is seen in the rapid tarnishing of silverware as soon as the furnace is lighted; by the occasional escape of furnace gas, detectable by its odor, or of smoke, which pervades the house. The general malaise and the headaches during the winter months are undoubtedly due in many instances to the presence of this gas.

Enormous quantities of carbon monoxid are daily produced in the manufacture of illuminating gas, producer gas, and water gas. Of the 60,000,000 cubic feet of street gas daily distributed in Chicago through the 3102 miles of mains, over 29 per cent. is carbon monoxid. During the past eleven years only once have any of the London gas companies exceeded the reasonable maximum of 20 per cent. of CO in the gas. The average has been about 12 per cent.²

The proportion of carbon monoxid differs greatly in domestic and industrial gases, varying between 4 and 30 per cent.; in coal gas 4 to 10 per cent., and 30 per cent. in water gas, and 20 and 30 per cent. in producer gas. Lime-kiln gases, waste gases from ammonia soda processes, and gases left in the track of explosions in coal-pits contain from 1.25 to 2.5 per cent.³ Wood gas made by the Wilkinson process was found to contain 33.75 per cent., while the commercial gas served to the consumer and made by mixing of gases from wood, coal, and naphtha contained 11.25 per cent.⁴ Almost all illuminating gas contains a large proportion of water gas, so that when this gas is discharged into an inhabited space it becomes exceedingly dangerous. An atmosphere containing 0.2 per cent. is capable of destroying life.⁵

The greatest percentage of carbon monoxid asphyxiation is through the medium of illuminating gas, which has the characteristic odor of the hydrocarbons accompanying the carbon monoxid gas. The familiar odor does not prevent many accidental poisonings, as the odor may not be perceived by those in deep sleep, or by a person with a defective sense of smell. It has been suggested that ethylene (C_2H_4), which is very poisonous to plants, might be the real cause of the gas

¹ Remsen, Carbonic Oxid as a Source of Danger to Health in Apartments Heated by Cast-iron Furnaces or Stoves, National Board of Health Bulletin, Washington, 1881, ii, No. 52, 857; J. Gottschalk, Ueber die Nachweisbarkeit des Kohlenoxides in sehr kleinen Mengen und einige Bemerkungen zu der sogenannten Luftheizungsfrage.

² Chem. Trade Jour., 1922, 70, 451.

³ Douglas Herman, Notes on Poisoning by Carbonic Oxid, Journal of the Society of Chemical Industry, 1896, 15, 857.

⁴ C. A. Doremus, Wilkinson's Process of the Manufacture of Illuminating Gas from Wood, Jour. Amer. Chem. Soc., 1880, ii, 449.

⁵ Haldane, Jour. Physiol., 1895, 18, 430-462.

TABLE I
ASPHYXIATIONS, 1912-1916

	Carbon Monoxid.	Water Heaters.	Acci- dental.	Undeter- mined. ¹	Suicides.	Homi- cides.	Totals.
1912							
January.....	29.48	1	14	8	13	0	36
February.....	28.65	0	13	3	12	1	29
March.....	29.18	0	8	5	17	2	32
April.....	29.50	1	14	1	18	0	34
May.....	29.29	2	7	10	20	0	39
June.....	29.29	0	7	6	11	2	26
July.....	28.73	1	5	5	17	3	31
August.....	28.97	0	6	2	8	1	17
September.....	28.80	0	2	3	15	0	20
October.....	29.26	0	12	9	8	0	29
November.....	29.54	0	14	4	9	0	27
December.....	29.20	0	22	5	20	1	48
1913							
January.....	29.26	0	9	3	13	0	25
February.....	29.30	0	14	4	9	0	27
March.....	29.57	0	20	9	7	0	36
April.....	29.33	0	6	3	20	1	30
May.....	29.77	0	12	7	17	0	36
June.....	30.01	0	17	5	11	1	34
July.....	30.76	0	5	1	17	0	23
August.....	29.79	0	7	3	10	0	20
September.....	29.88	1	16	4	15	0	36
October.....	30.09	0	9	8	17	0	34
November.....	29.97	0	11	12	7	0	30
December.....	29.94	0	8	9	9	0	26
1914							
January.....	28.6	0	10	2	24	0	36
February.....	28.6	1	8	6	18	0	33
March.....	24.5	1	13	8	15	0	37
April.....	27.5	0	9	8	11	2	30
May.....	22.7	0	10	12	19	0	41
June.....	22.7	0	2	6	11	0	19
July.....	27.1	0	4	1	8	1	14
August.....	27.1	0	7	4	14	0	25
September.....	26.8	1	4	7	28	1	41
October.....	25.5	0	18	11	28	0	57
November.....	26.6	0	10	4	15	1	30
December.....	26.6	0	13	16	15	0	44
1915							
January.....	30.1	1	6	4	20	0	31
February.....	30.1	2	14	12	15	1	44
March.....	29.8	0	15	5	26	2	48
April.....	29.2	1	14	6	19	3	43
May.....	25.2	2	10	7	17	0	36
June.....	30.5	6	11	7	25	0	49
July.....	27.8	0	6	3	30	0	39
August.....	27.8	3	2	6	19	2	32
September.....	25.4	1	7	7	17	0	32
October.....	27.8	1	17	11	19	0	48
November.....	27.0	0	13	9	20	1	43
December.....	24.9	0	20	13	13	1	47
1916							
January.....	23.9	1	16	9	23	5	54
February.....	26.4	1	13	7	13	0	34
March.....	24.1	0	18	7	21	0	46
April.....	23.9	0	19	8	19	0	36
May.....	27.2	2	14	8	23	0	47
June.....	26.2	2	11	2	12	4	31
July.....	23.0	0	5	12	20	4	41
August.....	24.2	0	5	4	12	0	21
September.....	22.4	0	13	8	26	3	50
October.....	22.6	0	23	9	17	1	50
November.....	29.1	0	7	5	20	0	32
December.....	31.0	0	14	6	13	2	35

¹ Undoubtedly many of the "undetermined" cases were suicides, the evidence being inadequate to warrant a verdict of suicide.

asphyxiation.¹ Using a mixture containing 50 per cent. ethylene, which is over six times that found in illuminating gas distributed to homes, McNally was unable to show other than a narcotic action upon mice and rats.

It is commonly believed that during the winter months the percentage of carbon monoxid increases, and that this is the chief reason for more deaths from gas poisoning. The percentage of carbon monoxid does not, however, increase during the winter. Table I gives the percentage of carbon monoxid and the number of deaths from gas asphyxiation for each month for the years from 1912 to 1916 inclusive, in Cook County, Illinois. The more extended use of gas in the homes during the dark and cold months of the winter and the closed doors and windows, preventing proper ventilation if there are leaky pipes or loose cocks, accounts for the increased number of asphyxiations. All gas stoves, plates, and heaters should be connected by metal instead of rubber. This precaution alone would save many lives.

The majority of deaths from carbon monoxid are due to the inhalation of illuminating gas. Table II shows how deaths from this poison have increased from 1905 to 1919. During 1920 there was a decided decrease in deaths from gas asphyxiation.

TABLE II

TOTAL GAS ASPHYXIATION CASES FOR THE SIXTEEN YEARS FROM 1905 TO 1920, INCLUSIVE

Asphyxiation by gas.	Acci- dental. ²	Undeter- mined. ²	Indus- trial.	Water Heaters.	Suicide.	Homi- cide.	Totals.
1905	59	55	..	..	83	7	204
1906	87	36	..	..	59	5	187
1907	76	61	..	..	74	1	212
1908	85	75	..	..	115	3	278
1909	102	81	..	..	107	12	302
1910	127	65	10	4	116	7	329
1911	103	66	4	7	115	2	297
1912	110	61	11	10	153	9	354
1913	148	64	..	1	163	3	379
1914	103	78	3	3	200	5	392
1915	126	93	5	17	242	6	489
1916	160	92	6	6	219	18	501
1917	167	85	10	3	193	12	470
1918	196	80	11	7	168	17	479
1919	222	56*	11	11	207	11	518
1920	199	41	5	11	127	3	386
1921	194	43	1	8	168	5	419

¹ Matthews, Physiological Chemistry, 1915, 495.

² The industrial gas cases and those by water heaters were included with the "accidental" and "undetermined" up to the year 1910.

The following is a typical analysis of gas from a city main:

	Per cent.
Carbon dioxid.....	5.00
Illuminants.....	8.40
Carbon monoxid.....	26.90
Oxygen.....	2.70
Hydrogen.....	31.20
Methane.....	11.20
Nitrogen.....	14.60

having a B.T.U. of 472 to 565.

From the records of death from carbon monoxid poisonings during 1918 and 1919, McNally found 52 causes for the inhalation of the gas.¹ In Table III there have been enumerated some of these causes, where they have produced three or more deaths, the chief one of which was "open jet, cause of jet being open unknown"; the next was "open burner of gas plate or range," and third, "the boiling over of water from a vessel, putting out the flame."

TABLE III²

	1918.	1919.
1. Open jet, cause of its being open unknown.....	86	133
2. Open burner of gas plate or range.....	48	44
3. Open burner of range, vessel boiling over.....	24	20
4. Deceased intoxicated.....	19	
5. Disconnected hose.....	17	29
6. Defective fixture.....	14	5
7. Lighted gas heater.....	10	6
8. Coal stove gas.....	8	1
9. Hot-water heater.....	7	11
10. Gas heater.....	6	6
11. Defective rubber hose.....	5	14
12. Automobile motor running in closed garage ²	5	2
13. Clothing hanging on fixture.....	5	
14. Wind blew light out.....	4	3
15. Coke gas from furnace.....	4	3
16. Disconnected pipe.....	4	2
17. Broken supply-pipe.....	4	1
18. Gas frozen.....	4	

Table IV shows where the deaths occurred, the majority of which took place in homes:

TABLE IV

	1918.	1919.
Gas cases in homes.....	263	272
Gas cases in hotels.....	10	17
Gas cases in plants or factories.....	12	8
Gas cases in garages.....	5	2
Gas cases on street (in wells).....	3	
Gas cases in railroad yards.....	1	
Gas cases in clubs.....		1
In city.....	275	289
Outside the city.....	19	11
Accidental and undetermined cases (male).....	215	215
Accidental and undetermined cases (female).....	79	85
Children fifteen years or under.....	7	28
Deceased seventy years or over.....	47	45

¹ See also Section on Industrial Toxicology, p. 791.

² See Henderson, Haggard, Teague, Prince and Wunderlich, Jour. Indust. Hyg., 1921, 3, 79, and 137; "Carbon Monoxid Poisoning in Closed Garages," Pub. Health Rep., 1921, 36, 2215. Fieldner, A. C., and Jones, G. W., Jour. Ind. and Eng. Chem., 1922, 14, 599.

Action.—Carbon monoxid may be freely respired, its presence in air not being manifested either by irritation to the air-passages or by its affecting the sense of smell, but the moment it comes in contact with the blood, by diffusion, it unites with the red pigment of the blood-corpuscles, forming a definite compound, carbon monoxid hemoglobin, exactly replacing the oxygen volume for volume.

According to the research of Nicloux,¹ one volume of carbon monoxid acts like 220 volumes of oxygen. The corpuscle is not dead. All it needs is oxygen under sufficient tension to displace the carbon monoxid. Hill² and Barcroft³ have demonstrated that carbon monoxid combines more readily with unsaturated oxyhemoglobin than with hemoglobin. Hemoglobin will take up more carbon monoxid at a given tension if a little oxygen is present than if oxygen is completely absent. Hufner⁴ found that 1 gm. of carbon monoxid hemoglobin contains 1.338 c.c. of carbon monoxid, computed at 0° C. and 760 mm. pressure. The oxygen absorbed from the air is normally taken up by the blood in the form of a loose chemical combination with the red coloring-matter (hemoglobin) of the corpuscles, and in this form it is carried to the tissues in which it is used. Oxygen and carbon monoxid combine chemically with hemoglobin in equal molecular proportions, and therefore, in equal volumes, the oxygen combination readily liberating its oxygen, while the carbon monoxid is relatively stable. Haldane believes that all the effects can be referred to lack of oxygen, the symptoms increasing with the saturation of the blood with carbon monoxid. Mice were kept alive on exposure to 200 to 300 times the fatal dose of carbon monoxid in the presence of oxygen under high pressure (1 to 2 atmospheres). Mosso repeated Haldane's experiment, using monkeys instead of mice, with the same result. The blood-corpuscles are not changed in form, though those found in the liver are, after a time, somewhat modified. Nicloux⁵ has shown that the red blood-cells, even when saturated with carbon monoxid, are not devitalized at all, but are ready to resume functioning when supplied with oxygen. The gas causes the blood to assume a color varying from violet to cherry red and both blood and foam are readily distinguished from normal arterial blood. Blood containing carbon monoxid hemoglobin may be deprived of the gas by submitting the blood to diminished pressure, or by passing the oxygen or air through it for a considerable length of time.

From observations on human beings some claim that this change may take place in a couple of hours, while others state in from four to six. Out of 43 consecutive gas cases received at the Cook County Hospital of Chicago, 34 per cent. were examined within one-half hour from the time the patient was removed from the source of exposure, carbon monoxid being found in all of these; in 30 per cent. the exact

¹ Presse méd., 1916, 25, 153; Ibid., 1921, 29, 701.

² Biochem. Jour., 1914, 7, 471-480.

³ Ibid., 481-491.

⁴ Arch. f. Physiol., 1894, p. 130.

⁵ Presse méd., 1921, 29, 701; Médecine, 1922, 3, 913.

time was not known, but was greater than one-half hour, 27 per cent. being positive and 3 per cent. negative. Twenty to forty minutes elapsed in 14 per cent., 12 per cent. gave positive tests and 2 per cent. negative; 10 per cent. were examined in three hours, all being positive; in another 10 per cent. five hours elapsed, all were positive, and in 2 per cent. twelve hours passed and all gave positive tests.

It is claimed that the carbon monoxid may be in part changed by oxidation into carbon dioxid within the body (Gruber). Others, among them Gaglio, claim that this oxidation does not take place, but that the carbon monoxid is voided, quantitatively, unchanged.¹ Carbon monoxid when injected into the abdomen or swallowed, dissolved in water, also produces poisonous effects as if inspired. The blood is, however, never fully saturated, and some of the gas may diffuse from the corpuscles into all the tissues; indeed, it has been shown by Fehling, from the mother to the fetus. This raises the question of whether a corpse may not absorb the gas from the atmosphere and thus give indications of carbon monoxid poisoning when death has been due to other causes. The experiments of Strassmann and Schulz² have demonstrated that carbon monoxid may penetrate by diffusion all parts of the cadaver, with sufficiently long exposure in air containing carbon monoxid.

The question as to whether carbon monoxid has any direct action upon the nervous system has been the subject of much dispute. The inhalation of oxygen with at least 20 per cent. of carbon monoxid seems to affect the nervous system, since violent disturbances of the system with cramps and total paralysis of the limbs appear within the first minute of inhalation while the blood could certainly not have become sufficiently saturated with the gas by that time to produce such symptoms. Kobert, Geppert, and others strongly incline to the belief in an action upon the nervous system, both of the peripheral nerves and of the ganglion-cells of the brain, from the symptoms produced and the pathologic appearances, and they extend the poisonous action of the gas to the production of a degeneration of the muscles and glands.³ Haggard has demonstrated that this gas has no direct toxic action upon nervous tissue.

People nearest to the doors or windows in a room into which illuminating gas is escaping suffer the least, and those nearest the floor the most.

CASE 1.—December 22, 1906, E. F. and a woman went to a rooming house at 4 P. M. At 5 P. M. the landlady noticed the odor of gas coming from the room. As no one responded when she knocked at the door, entrance was gained from the transom. The man was found dead. The woman, still breathing, was removed

¹ Concerning the elimination of carbon monoxid, consult L. de Saint-Martin, *Recherches sur le mode d'élimination de l'oxyde de carbone*, *Comptes Rendus*, 1891, cxii, 1232; 1892, cxv, 825.

² *Berl. klin. Wehn.*, 1904, xli, 1233; Wachholz u. Limburger, *Vrtljschr. f. ger. Med.*, 1902, 3 F., xxiii, 223.

³ Kobert, *Lehrbuch*, 1906, ii, 871; also Kobert, *Practical Toxicology*, English translation, L. H. Friedburg, New York, 1897; Haggard, H. W., *Amer. Jour. Physiol.*, 1922, 60, 244.

to a hospital, where she recovered. The woman was on the inside of the bed, near a window. A gas heater was found in the room with two burners still lighted, and three unlighted burners from which gas was escaping.

CASE 2.—February 12, 1915, C. W. and roommate were found in a room unconscious from gas escaping from a defective hose on a gas heater. The roommate, who was nearer to a window, recovered.

CASE 3.—March 16, 1916, F. M. A. died from gas escaping from a defective heater. The roommate on the inside of the bed nearer the window recovered.

Many other cases could be cited from our records, but the foregoing are typical, and the first case illustrates that a person can be asphyxiated in a room where a gas burner or jet is lighted.

Lethal Dose.—Since the poisonous action of this gas was noticed in 1802 by Guyton de Morveau and submitted to personal experiment by Sir Humphry Davy, a large number of experiments have been made on men and animals and observations recorded from the results of accidents. It would appear from these that about 0.8 gram (about 12 gr.) of carbon monoxid is fatal to a man of 70 kilos (154 lbs.), 11.5 milligrams per kilo being fatal to rabbits. From this it would appear to be less poisonous than hydrocyanic acid. Nevertheless, extremely small portions when breathed produce unmistakable symptoms of poisoning. According to Gruber, 0.02 per cent. is the limit of toxicity, while at 0.05 per cent. symptoms were clearly observable.¹

Exposure to a contaminated atmosphere for two or three minutes may cause serious illness. Burrell² found that exposure for twenty minutes to air containing 0.25 per cent. of carbon monoxid made him sick for eight hours after the exposure. Air containing as little as 0.1 per cent. of carbon monoxid when breathed for several hours produced headache and vomiting with some members of the Bureau of Mines, while others were not affected. An exposure of ten minutes in a cellar has killed a person.³ Two men in a cooper shop fire in Chicago, June 7, 1917, went into the burning building to recover their tools. In thirty minutes both were found dead. Examination of the blood showed that death was due to carbon monoxid asphyxiation (from smoldering wood).

It is especially noticeable that all animals do not behave alike. In some, as birds and chickens, convulsions or cramps are caused, while this effect is not noticed in mice or rabbits. Gruber found that rabbits behaved abnormally in an atmosphere containing between 0.07 and 0.08 per cent. As soon as the quantity reaches 0.1 per cent. the poisonous effect is produced, while with 1 per cent. the toxic action is rapid. Gruber breathed air containing 0.021 to 0.024 per cent. of carbon monoxid for over three hours without experiencing any unpleasant sensations. He states that the blood of the entire body is capable of containing 1 liter of oxygen or 1 liter of carbon monoxid. The quantity of carbon monoxid breathed by him amounted in total to 300 c.c., but being distributed over a considerable length of time,

¹ Max Gruber, Ueber den Nachweis und die Giftigkeit des Kohlenoxyds, und sein Vorkommen in Wohnraeumen, Arch. f. Hygiene, 1883, vol. i, p. 145.

² Burrell and Seibert, Miners' Circular 14, Dept. of Interior, Bureau of Mines, Washington, 1914.

³ Coullaud, Ann. d'hyg., 1909, Series 4, 12, 490.

did not produce poisonous effects. Frogs placed by him in an atmosphere of pure carbon monoxid lived over ten hours. Worms survive many hours' exposure to this gas.¹

The rapidity of the action has been established by many observations. Birds die instantly in an atmosphere containing 5 per cent., while dogs, rabbits, and other animals are killed in times varying from a minute or so to half an hour, according to the amount of this gas in the atmosphere.²

The speed with which carbon monoxid acts is illustrated by a case given by Sonnenschein of a chemist who, by a single breath of an atmosphere laden with this gas, fell backward as if struck by lightning. He recovered after a quarter of an hour's serious symptoms through timely aid.³

Henderson and Haggard⁴ from their studies have arrived at a standard for calculating the toxic action of carbon monoxid, which refers to the concentration of the gas and the time of exposure to it. When the time of exposure in hours multiplied by the concentration of CO in parts per 10,000 of air equals 3 there is no perceptible physiologic effect; when it equals 6, there is a just perceptible effect; when it equals 9, headache and nausea are induced; and when it equals 15 or more the conditions are dangerous to life.

Duration.—In the majority of cases the victims are found dead or die a short time afterward. Fishbein⁵ reports a patient living five days; Long and Wicki,⁶ thirty-six days; Sibelius,⁷ three months. McNally has examined the blood of several patients who lived two days and one who lived four days after exposure to illuminating gas. Recovery is usually complete within a week, but after-effects may persist for weeks and months. O'Malley⁸ reports a case of a woman who, poisoned by illuminating gas, did not regain her mental faculties for three months. He refers also to a case cited by Brouardel, namely, that of a physician poisoned by carbon monoxid, who lost his memory, this amnesia lasting eighteen months, at the end of which time he fully recovered.

There are few references in toxicologic literature to homicidal poisoning unaccompanied by simultaneous suicide by illuminating gas, or gases containing carbon monoxid.

CASE 4.—December 14, 1916, Mrs. B. turned on the gas, killing her two children. Her husband had committed suicide the previous day. The woman was found to be insane and was committed to an asylum.

CASE 5.—June 26, 1917 a mother killed her baby with gas, attempting suicide. She was held for murder.

¹ Jordan, H., and Schwarz, B., *Arch. ges. Physiol.* (Pflüger's), 1920, 185, 311.

² Woodman and Tidy, *Forensic Medicine and Toxicology*, Philadelphia, 1877, p. 485.

³ F. L. Sonnenschein, *Handbuch der ger. Chemie*, Berlin, 1869, p. 288.

⁴ *Jour. Ind. and Eng. Chem.*, 1922, 14, 229.

⁵ Fishbein, Morris, *Illuminating-gas Poisoning*, *Jour. Amer. Med. Assoc.*, March 8, 1913, lx, 737.

⁶ Long and Wicki, *Rev. méd. de la Suisse romande*, 1902, 22, 172.

⁷ Sibelius, *Ztschr. f. klin. Med.*, 1903, 49, 111.

⁸ O'Malley, *Amer. Jour. Med. Sci.*, 1913, 145, 865.

Carbon monoxid poisoning may be of interest in civil cases, for instance, under conditions in which death is a form of chronic poisoning and the results amount to criminal negligence on the part of another.

In another case, the estate of *Catchman Olsen vs. City of Chicago*,¹ the widow was given a verdict of \$3500, the death of Olsen having been proved to be due to a leaky gas-pipe in one of the repair shops of the city. When an insurance policy is involved it is of the utmost importance to show the presence of carbon monoxid by chemical examination, and to prove whether the case is a murder, a suicide, or an accident, as a policy may be void in the case of a suicide. The origin of the poisonous gas may usually be found from the surroundings, as an open gas-jet or a leak in the feed pipes. A loose-fitting stopcock of many a gas-jet may be opened by careless persons throwing their wraps over a wall gas-bracket or over the gas fixture suspended from the ceiling. Several cases of such carelessness were investigated by the coroner's office of Cook County, Illinois, during 1916. At inquests it is frequently desirable to distinguish between poisoning by coal gas, illuminating gas, or other source. At the present time there are no good analytic methods by which we can distinguish illuminating gas poisoning from that due to coal fumes. Wachholz² has suggested that the presence of hydrocyanic acid in the blood, and Cruz³ that the presence of hydrocarbons in the blood gases would identify the source of the carbon monoxid as being illuminating gas. An investigation of the room for the source of the carbon monoxid will give more definite results than a chemical examination of the blood gases.

In one case investigated a medical student had been overcome by carbon monoxid from a smoking oil-stove on which he was cooking his meals. The room, free from gas fixtures, was covered with soot. In three different instances a closed stovepipe damper caused the coal-gas fumes to enter the room and produce death by carbon monoxid gas.

Two or more persons may be exposed to a contaminated atmosphere; one or more may die, while the others recover.

Three young physicians in Melbourne, after playing tennis, went to bathe in a shower bath, in which the water was heated by a gas-burner. Half an hour later a messenger found one dead and two unconscious.⁴

January 5, 1917 three men were found unconscious in a room. One man died, the other two recovered. A stovepipe had parted from a hard coal burner, allowing the carbon monoxid to escape into the room. The blood of the man who died was 45 per cent. saturated with carbon monoxid.

The time required to eliminate completely carbon monoxid by respirations of pure air has not been determined definitely. It varies greatly with different patients, the carbon monoxid hemoglobin

¹ Olsen *vs.* City of Chicago, Decision on Review, vol. 697, Book 2, Case 262, April 30, 1914.

² Wachholz, *Ztschr. f. med. Beamte*, 1896, 9, 400.

³ Cruz, *Ann. d'hyg.*, 1898, Series 3, 39, 385.

⁴ Australian letter, *Lancet*, London, 1911, 2, 1102; see also Darling, *Med. Jour. Australia*, 1918, 2, 181.

apparently not being in all cases under sufficient tension with oxygen to liberate readily the carbon monoxid. Henderson¹ states that carbon monoxid is practically eliminated in three or four hours. The experiments of Michel² tend to show that it does not exceed a few hours; Koch³ states that he has found it after ten hours; Pouchet⁴ after sixty hours; Fishbein after five days; Wachholz⁵ after seven days. In specimens of blood submitted to McNally from 2 cases ending fatally in two days, and one of four days' duration, he was able to detect carbon monoxid hemoglobin. He has had over 100 cases of over four hours' standing, in which he could detect carbon monoxid by definite color tests and the palladous chlorid method. In a large number of his cases of gas poisoning, with clear histories of attempted or consummated suicide by means of illuminating gas, the blood failed to show the presence of carbon monoxid after the respiration of pure air and oxygen for a few hours. Blood from suicides who died within a half-hour after being discovered in a gas-filled room contained as high as 13.6 per cent. of carbon monoxid by volume. Blood from other cases in which life was prolonged for a couple of hours contained from traces to 5.5. per cent. carbon monoxid.

The compound of carbon monoxid hemoglobin can be dissociated by hydrogen and carbon dioxid as well as with oxygen. Gaglio⁶ demonstrated that carbon monoxid inhaled by an animal may be recovered from the expired air with a loss of only 2.8 per cent., due to experimental conditions. The odor of illuminating gas has frequently been noticed in the expired air of patients after being taken to a hospital. Nicloux states that he has found carbon monoxid in normal blood of dogs and in human blood. The amount found in the blood gases of dogs living in Paris varied from 0.08 to 0.18 per cent. Using the method of Fodor, McNally has failed to find carbon monoxid in the blood of dogs and in normal human blood. Buckmaster and Gardner⁷ failed to find carbon monoxid in the blood gases of cats.

Symptoms.—Unless accidental, pure carbon monoxid poisoning is rarely met with in the human subject, but since many of the gaseous mixtures contain a high proportion of the gas, the other gases being of a less toxic character, we may fairly assume the symptoms in these cases to be due to carbon monoxid. A large number of experiments on animals made to breathe carbon monoxid, diluted with either oxygen or air, have resulted in showing that the blood-pressure is at first considerably increased as the result of the stimulation of the vasomotor center. A benumbing of this center is then shown by the decrease of the pressure and a distention of the blood-vessels. Apoplexy may

¹ Henderson, Yandell, Carbon Monoxid Poisoning, Jour. Amer. Med. Assoc., August 19, 1916, lxvii, 580.

² Michel, Vrtljschr. f. gerichtl. Med., 1897, 14, 36.

³ Koch, Diss., Greifswald, 1892.

⁴ Pouchet, Ann. d'hyg., 1888, 30, 361.

⁵ Wachholz, Vrtljschr. f. gerichtl. Med., 1902, 23, 231.

⁶ Gaglio, Arch. f. exper. Path. u. Pharmacol., 1887, 22, 235.

⁷ Buckmaster and Gardner, Jour. Physiol., 1910, 41, 60, 246; Proc. Roy. Soc., 1909, 81, 516.

result from the first stage. More or less extended patches of bright color, especially on the anterior portion of the body, make their appearance and are distinctly different from the violet-red patches that appear, postmortem, especially on the dependent portions of cadavers. The pulse becomes slower when the blood-pressure rises, and a violent beating of the heart is experienced.¹ Subsequently the pulse becomes frequent, but small. Breathing is deep and difficult, and, as a result of deficient oxygenation, a diminished production of carbon dioxide occurs.² Respiration ceases when the respiratory center is paralyzed, but the stage of stimulation is protracted. The muscular system is very generally affected, in which case the extremities may fail to perform their functions for many days, or special muscles or muscle groups become paralyzed and afterward degenerate. Sensation to pain may be absent or remain suspended for a long time. The sensations are headache, throbbing of the temples, singing in the ears, faintness, dizziness, and vomiting. The face becomes red, and there is loss of memory, vertigo, fainting, anesthesia, and loss of all spontaneous power of movement, together with tonic and clonic spasms. The heart's action is at first violent in the stupor, then weak, slow, and arrested. The bodily temperature is lowered. Involuntary discharge of feces, urine, and seminal fluid is not infrequent.

The recovery is sometimes rapid. Men working around gas-mains, in ditches, will be affected, but when taken into the air or given a drink of whisky or other stimulant speedily recover and return to work. As a rule, however, there is a slow return to consciousness, with more or less prolonged headache, nausea, and weakness. Symptoms may continue for several days. Where the gas has been inhaled for a considerable time, the red patches on the skin will remain for quite a while. The paralysis and anesthesia begin in the lower extremities and rise to the trunk. The loss of power and of sensibility is frequently shown by the severe burns received by a person falling on a gas- or other stove or brazier. Loss of consciousness is often sudden. At other times there is a slowly increasing drowsiness. There is a great similarity in the symptoms to those of drunkenness. Recovery may in some cases follow a protracted sojourn in a not too poisonous atmosphere, while others, after an hour or two's inhalation, cannot be brought to life. While most have no remembrance of the symptoms, many claim to have suffered greatly. Death follows from paralysis of the respiratory apparatus.³ When the gas itself does not kill, apoplexy or softening of the brain may follow. Pneumonia not infrequently follows the intoxication (see p. 411). According to Becker and Schwerin, the sequelæ divide themselves into four groups: (1) Primary gangrene⁴ with blisters and decubitus. (2) Primary hemorrhages, as of the lungs, apoplexy, and the like. (3) A persistent distention of the capillaries

¹ See Haggard, *Amer. Jour. Physiol.*, 1921, 56, 390.

² Henderson and Haggard, *Jour. Pharm. and Exp. Therap.*, 1920, xvi, 11.

³ See Logan, *Jour. State Med.*, 1920, xxviii, 306.

⁴ See Briggs, *Jour. Amer. Med. Assoc.*, 1919, 73, 678; Girault et Richard, *Presse Medicale*, Paris, 1922, 52, 30.

and other vessels in which the symptoms are shown in the skin, red nose, red spots not unlike those caused by frost-bite. (4) A deep-seated disturbance of the regeneration of all organs, especially of the vascular walls and the ganglion cells of the nervous system, evidenced by secondary hemorrhages, idiocy, imbecility, chorea, ascending paralysis, etc. Indeed, the results of this variety of poisoning are manifold, reminding one of diseases of the brain, spinal cord, lungs, kidneys, liver, or skin. Diagnosis is difficult.

Chronic poisoning by carbon monoxid has received the attention of many observers in recent years. There is very good evidence of this form. Accumulated cases show that it is the result of being in a constantly contaminated atmosphere. The symptoms are described as an alteration in the digestion, diminished vigor, gray color of the skin, coated tongue, loss of memory, diminution of the psychic powers, and occasional convulsions. The pathologic findings of autopsies have shown, in some cases, fatty degeneration; in others, pernicious anemia. Forbes¹ quoting Dr. Davis, chief surgeon of the Illinois Steel Company, reports that in investigating carbon monoxid poisoning in blast furnace workers, he fails to find evidence of anemia resulting from frequent exposure to carbon monoxid; 64.1 per cent. of the red blood-cell counts were over 5,000,000, 2.2 per cent. over 6,000,000, and none were under 4,000,000.

Haines, Karasek, and Apfelbach,² in their investigations of the effects of carbon monoxid, found that workmen exposed frequently to the gas in metallurgical establishments in a large majority of cases developed a considerable increase of red corpuscles above the normal, the number in one case examined reaching 9,000,000. The amount of hemoglobin was also usually above normal. These investigators attribute the increase in red cells and hemoglobin to a protective effort on the part of the system. The same investigators also found that workmen frequently exposed to carbon monoxid in metallurgical establishments showed more or less muscular weakness, as was demonstrated by tests with a hand dynamometer, a comparison being made with an equal number of workmen of the same social grade employed in industrial establishments in which they were not exposed to the gas.

Gruber³ has shown, along with others,⁴ that carbon monoxid is not a cumulative poison, but that when inhaled in very small quantities it disappears from the blood. In cases of chronic poisoning the blood does not serve for diagnosis. This is not the case, however, in acute poisoning, where a timely examination of the blood taken from the patient as soon as possible will indicate the poisonous effect of carbon monoxid and lead to the adoption of proper methods of resuscitation.

¹ Jour. of Industrial Hygiene, May, 1921, 3, No. 1, 13.

² Report of [Illinois] Commission on Occupational Diseases, 1911, p. 89.

³ Arch. f. Hygiene, 1883, 1, 145.

⁴ A Study of the Poisonous Effects of Coal and Water-gas, by W. T. Sedgwick and W. R. Nichols, Sixth Annual Report of the State Board of Health and Charity of Massachusetts, Boston, 1885; Henderson, Jour. Amer. Med. Assoc., 1916, 67, 580; and Haldane, Jour. Physiol., 1895, 18, 201.

As a further aid to diagnosis, the comatose condition, low temperature, absence of odor of alcohol, loud snoring, and bright-red appearance of the face would lead one to suspect gas-poisoning, especially if the body were found in a closed room or in a confined space with indications of gas-poisoning more or less apparent. As a further diagnosis the urine is found to contain a reducing substance, generally glycuronic acid, and in many cases there is albuminuria. Red patches or spots upon the surface of the skin are characteristic. Legry and Lermoyes¹ have shown that the blood in the cerebrospinal fluid may reveal carbon monoxid long after it has disappeared from the blood-stream.

Treatment.—This consists in taking the person at once out of the poisonous atmosphere into fresh air, and in inducing artificial respiration as rapidly as possible; the giving of oxygen under slight pressure, enough to distend the cheeks, and then compressing the lungs, is considered one of the most, if not the most, efficient method of restoring the person to life. A small amount of carbon dioxid with oxygen has been recommended.² Unfortunately, the cost of the oxygen is apt to restrain it from being used in sufficient quantity. If the body possesses an abnormally low temperature, artificial warmth is needed. Cold affusions to the head, injection of iced water, friction, mustard baths, faradization of the phrenici, or stimulation with ammonia are simple expedients. Hydrogen dioxid and ozone, though recommended, have not been found efficient as antidotes. The recovery of at least one case³ of gas poisoning is, however, attributed to the prolonged use of the former, it being given in doses of 2 to 3 ounces, diluted with water, both by the stomach and as an enema. Black coffee and alcoholic stimulants may be given if the person can swallow. Transfusion of the blood has been recommended,⁴ but has not proved very satisfactory. Injection of alkaline salt solution directly into the veins, or according to more recent practice, into the rectum, the body being placed in the position of auto-transfusion, recommended by Jersey, has been often resorted to. Venesection of from 6 to 12 ounces precedes the introduction of the salt solution.⁵ The frequent occurrence of accidents known as "gassing" has led to having compressed oxygen at hand in works, mines, and other establishments. Experience has shown that a single person is, as a rule, not able to rescue any one overcome.⁶

In cases of carbon monoxid poisoning or in asphyxia from other causes, such as drowning, reliance has been placed in some quarters on

¹ Presse méd., 1920, xxviii, 816.

² Henderson and Haggard, Jour. Pharmacol. and Exper. Therap., 1920, 16, p. 11; Haggard and Henderson, Jour. Amer. Med. Assoc., 1921, 77, 1065; Forbes (Jour. Ind. Hyg., 1921, 3, 11) shows that recovery is three times as rapid when oxygen and CO₂ are given as when oxygen alone is administered. Henderson and Haggard, Jour. Ind. and Eng. Chem., 1922, 14, 229; Jour. Amer. Med. Assoc., 1922, 79, 1137.

³ C. J. Lind, Northwestern Lancet, February 15, 1902, 22, 70.

⁴ Burmeister, Jour. Amer. Med. Assoc., 1916, lxvi, 164, recommends resuscitation by means of preserved living erythrocytes.

⁵ W. T. Bull, Med. Record, New York, 1884, 25, 6.

⁶ The Use of Oxygen in Rescue Work in Collieries, American Gaslight Journal (from the Colliery Guardian), 1897, lxvii, 108; George Davis, Handbook of Chemical Engineering, 1902.

the use of the pulmotor. This is nothing more than an apparatus for inducing artificial respiration by mechanical means. Concerning its use it is to be said that it is probably no more efficient than are other means, properly applied, of bringing about artificial respiration and, further, the time spent in trying to obtain the apparatus would much better be employed in careful and strenuous manipulations by the most approved methods in the endeavor to produce renewed respiration, as the elements of time and prompt action are essential to the resuscitation of the individual overcome.²

The gas mask perfected and used by the U. S. Army² should be a part of the equipment of ambulances and every piece of fire apparatus, so that firemen who are forced to enter burning buildings may have protection against noxious fumes.

The principal features as given by Dewey are:

1. A canister of metal containing both neutralizing and absorptive chemicals and a smoke filter. The air to be breathed passes in through an inlet check valve and through chemicals and smoke filter.

2. A flexible rubber hose through which the purified air passes from the canister to the face-piece.

3. A face-piece effectively covering the eyes, cheeks, lower forehead, nose, mouth, and chin, provided with eye-pieces permitting vision and a harness to hold the face-piece in place when wearing the mask.

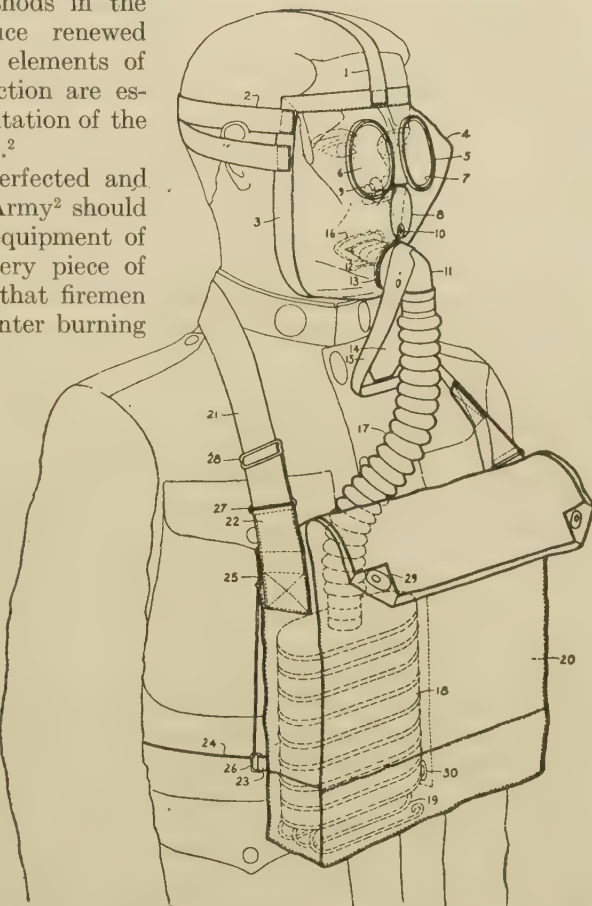


FIG. 39.—Diagrammatic cross-section of the gas mask: 1, Cotton tape; 2, elastic tape; 3, binder; 4, face-piece; 5, eye cup; 6, lens; 7, lens washer; 8, nose spring; 9, nose pad; 10, nose rivet; 11, die casting; 12, die casting nut; 13, die casting washer; 14, flutter valve; 15, flutter guard; 16, mouthpiece; 17, hose; 18, canister; 19, spring; 20, knapsack; 21, shoulder strap; 22, large loop chape; 23, small loop chape; 24, body cord; 25, eyelet; 26, small loop; 27, large loop; 28, center bar slide; 29, "Lift the dot" fastener; 30, grommet.

¹ See chapter on Death from Asphyxia, p. 386.

² Dewey, *Jour. Indust. and Engin. Chem.*, 1919, 11, 185.

4. An exhalation valve which affords easy discharge of exhaled air and at the same time instantly closes upon inspiration.

5. A knapsack slung from the neck or shoulder, in which the mask and canister are carried. In the box respirator type manufactured, the inhaled air, passing through the canister and hose, went directly into the mouth through a rubber mouthpiece, which in this manner offered protection to the lungs in the event of the failure of the fit of the face-piece or of damage to the face-piece. At the same time the mask was provided with a spring and rubber device which closed off the air-passage through the nose and compelled breathing entirely through the mouth.

It is also worth while to enumerate a few of the principal requirements to be fulfilled by a respirator.

1. It must successfully remove all gas fumes or smoke from the air to which a soldier is exposed, and must do this for the maximum of time for which the person is liable to be on duty.

2. It must be reasonably comfortable to the wearer.

3. The fit of the face-piece around the face must be a perfect gas-tight joint.

4. The material of the face-piece must be substantially impermeable to all noxious gases.

5. The eye-pieces must be strong and provide for good vision.

6. The complete equipment must have durability, for all personal equipment of a soldier in the field receives extremely hard usage.

7. The resistance to flow of air through the various parts must be kept at a low figure in order that the fighting efficiency of the individual may not be too much reduced.

8. It must be of minimum weight and bulk.

The points mentioned indicate but few of the severe requirements which had to be met during the course of production. All of them were not apparent in the early days, but became of importance and had to be met as the war progressed.

The canister filled with hopcalite (MnO_2 50 per cent., CuO 30 per cent., Co_2O_3 15 per cent.) acts as a catalyst oxidizing the carbon monoxid readily, when the contaminated air has been dried by passing over calcium chlorid.¹ The efficiency and life of the canister depends upon the life of the drying agent. When the canister gained more than 35 grams above the original weight, it should be withdrawn, as it then failed to act as a catalyst. The higher the temperature, the longer the life of the canister, as the hopcalite is less sensitive to water vapor at higher temperatures.

Workmen around blast furnaces are always exposed to carbon monoxid poisoning.² After passing the gas through the washers, where

¹ Lamb, Bray, Frazier, *Jour. Indust. and Engin. Chem.*, 1920, 12, 213; see also Rogers, Piggot, Bahlke and Jennings, *Jour. Amer. Chem. Soc.*, 1921, 43, 1973, and Merrill and Scalione, *Ibid.*, 1922, 44, 738.

² Watkins, *Tech. Paper*, 156, 1917, Dept. of the Interior, Bureau of Mines; Forbes, *Jour. Ind. Hyg.*, 1921, 3, 11.

it is freed from its suspended matter, it is usually invisible and practically odorless. The men working around the blast furnaces receive some warning (odor and dusts), of its presence when it escapes, while those working in places where the washed gas is being used fail to recognize the presence of the carbon monoxid. The gas mask with the hopcalite would prevent many asphyxiations in these workers.

The consensus of opinion at this writing seems to be in favor of the use of oxygen in carbon monoxid poisoning, and especially of having the remedy at hand in all works where operatives are exposed to noxious atmospheres. It is reported that no case of suffocation, though cases have been numerous, has proved fatal since the introduction of the oxygen bottle.¹

In one case a man was overcome by the backdraft from a blast furnace in the course of charging. Pure oxygen was introduced through the nose. He recovered consciousness and walked home. No details were printed.

In another case oxygen restored consciousness, though bleeding, electricity, injections, friction, and attempts at artificial respiration had failed.²

Blake³ reports that 3 out of 4 men overcome by coal-gas were restored by oxygen. The inhalation of oxygen, especially mixed with CO₂, prevents the headache subsequent to poisoning.⁴

Postmortem Appearances.—Poisoning by a small amount of carbon monoxid may produce very few changes, or if the patient lives for a number of hours after exposure, only a careful examination of the blood will reveal the presence of the gas. Where the blood is well saturated with the gas, the surface of the body is cherry-red. The eyes are closed and the countenance usually composed. The dependent parts at the surface of the body are of deeper red than other parts. There are frequently bright red patches upon the thighs and the front of the trunk and neck. The most characteristic change is the bright cherry-red blood, usually fluid and coagulating slowly, present in the arteries, veins, and all of the tissues. Blood of cats gassed with carbon monoxid showed no constant change of coagulation time.⁵ The brightness of the carbon monoxid hemoglobin may be masked by carbon dioxid from the fumes of coal-gas or from the smoke of burning wood or other combustible material. When death occurs rapidly from cyanid poisoning, the blood is also bright red, but the color is not as permanent as in gas poisoning, changing to blue on exposure to air. If the gas poisoning be prolonged, small hemorrhages are present in the pleural cavities, with pulmonary edema and bright red froth in the air-passages. The gastric and intestinal mucosa may also have small punctiform

¹ Douglas Herman, Notes on Poisoning by Carbonic Oxid, Jour. Soc. Chem. Industry, 1896, xv, pp. 854-858.

² Douglas Herman, On Poisoning by Gas; its Prevention and Cure, Jour. Soc. Chem. Ind., 1896, xv, 247.

³ Blake, Boston Med. and Surg. Jour., 1872, vol. lxxxvii, p. 149

⁴ See Sayers and O'Brien, Reports of Investigations, 2304, U. S. Bureau of Mines, 1921; Henderson and Haggard, Jour. Amer. Med. Assoc., 1922, 79, 1137.

⁵ Forbes and Hompe, Jour. Ind. Hyg., 1921, 3, 213.

hemorrhages. Occasionally, rather large hemorrhages are met in the great omentum and in the leptomeninges under conditions difficult to explain, except under carbon monoxid poisoning. The hemorrhages in the omentum are as large as the open hand.¹ The hemorrhages in the brain are never in sufficient degree to cause compression. A very characteristic change in prolonged carbon monoxid poisoning is the occurrence of punctiform hemorrhages and softening in the cortex and central nuclei of the brain, notably in the two internal segments of the lenticular nucleus.² The kidneys may show fatty degeneration and necrosis in the convoluted tubules. Where life has been prolonged, the skin may show herpes, blebs, and pemphigus followed by gangrene.³ Polycythemia and leukocytosis are quite regularly present, though a mild chronic poisoning may induce an anemia. Czoniczer⁴ has shown the presence of uricacidemia in carbon monoxid poisoning. Glycosuria is present in about 20 per cent. of the cases of gas poisoning, including those that die of carbon monoxid and those that recover.

Stevenson⁵ reports a case where the condition of the viscera was phenomenal, the rosy hue being visible after seventeen months. This is also the case with blood, which a great many observers say retains its color for several years, observations which Doremus confirmed by his own experiments.

Otto⁶ states that Landois was able to detect carbon monoxid in the body of a woman eighteen months after death. The blood retained its red color notwithstanding the fact that the body had undergone extreme putrefaction. Otto himself preserved the blood for two years by keeping it in a closed vessel.

Tests.—Carbon monoxid may be detected in the air through the absorbent power of a solution of cuprous chlorid in an excess of hydrochloric acid or an excess of ammonia. In either liquid it is completely absorbed. When large quantities exist, the diminution of the volume of the air passed through this reagent may be observed, but generally large volumes of the air have to be drawn through the solution, and the presence of the gas determined either by heating the solution to boiling, which causes its expulsion, or by dropping the same into a bright red solution of palladous chlorid, whereby a black precipitate of metallic palladium is produced ($\text{PdCl}_2 + \text{CO} + \text{H}_2\text{O} = \text{CO}_2 + 2\text{HCl} + \text{Pd}$). Doremus was able to detect the carbon monoxid generated by the burning of a smokeless fuel by the former method, absorbing the gas in cuprous chlorid solution, and afterward expelling it. Tests were applied, and the gas found to burn with a pale-blue flame. Care must be taken in using the palladium solution to exclude the presence of hydrogen

¹ Le Count, E. R., Personal communication.

² Kolisko, Beiträge zur gerichtlichen Medicin, 1914, 2; Photaxis, B. A., Anatomical Changes in the Central Nervous System Following Carbon Monoxid Poisoning, Vierteljahrs. ger. Med., 1921, 62, 42.

³ Mott, Brit. Med. Jour., 1917, i, 637; Hill and Semerak, Jour. Amer. Med. Assoc., 1918, 71, 644.

⁴ Münch. med. Wehnschr., 1920, lxxvii, 1121.

⁵ Guy's Hospital Reports, 1889, 46, 223.

⁶ Anleitung zur Ausmittlung der Gifte, 7th ed., Braunschweig, 1896, p. 262.

sulphid, ammonium sulphid, ozone, or hydrogen. The cuprous solution is especially valuable in determining the carbon monoxid in illuminating gas.

Carbon monoxid may be burned to carbon dioxid, but this method is open to error through the presence of hydrocarbons.

Gruber¹ prefers to absorb carbon monoxid from air by blood, using Fodor's² method modified. From 10 to 20 liters of the suspected air are shaken with slightly diluted blood for 15 minutes. The blood is then placed in a small flask and heated to boiling. Air, purified by being passed through a solution of palladous chlorid, is drawn through the heated blood and is conducted through solutions of lead acetate, dilute sulphuric acid, and finally palladous chlorid. A black precipitate in this indicates reduced palladium, and, therefore, the presence of carbon monoxid in the air tested. Fodor claims to be able to detect 1 part of carbon monoxid in 20,000 parts of air, in which he is corroborated by Gruber. Marsh-gas and other hydrocarbons do not interfere with the test as thus conducted. The test indicates quantities of carbon monoxid below the limit of toxicity (see p. 304). The quantity of palladium reduced may be determined by dissolving it in aqua regia and titrating with potassium iodid. Desgrez and Labat³ employ strips of filter-paper saturated with a 10 per cent. solution of palladous chlorid for the detection of carbon monoxid in the air, the depth of darkening of the sensitive paper giving a clue to the relative amount present.

Vogel⁴ uses diluted blood solution and examines the spectrum. Thus, by shaking diluted blood with from 100 to 200 c.c. of air and examining by the spectroscope, 2.5 per cent. may be detected. This represents a highly poisonous quantity. For lesser quantities 20 liters of air may be shaken with 10 c.c. blood, which is then tested according to Fodor's method. The wash-water from the bottle in which the air was shaken may be used for the spectroscope, whereby 1 to 0.05 per cent. of carbon monoxid is detectable.

This latter test has the advantage of enabling the experimenter to submit the blood to further tests, yet of preserving the wash-water, with its characteristic action in the spectroscope, in a sealed tube as an exhibit. Carbon monoxid hemoglobin imparts to blood a characteristic pink color, even when only a small proportion of the gas is present. Five tenths c.c. of the unknown sample of blood and a like amount of the normal blood are diluted to 100 c.c. in a cylinder. The normal blood will have a buff-yellow tint and the sample, if it contains carbon monoxid, will have a pink color. In testing for carbon monoxid in a contaminated atmosphere, a tube or cylinder containing the diluted normal blood is taken to the place where the air is to be examined. The normal blood is poured out into another tube, so that the air takes the place of the blood. The normal blood is then added to the tube, corked

¹ Arch. f. Hygiene, 1883, vol. 1, p. 145.

² Deutsch. Vierteljahresschr. f. öffent. Gesundheitspflege, 1880, vol. xii, Pt. iii. 377.

³ Ann. Chim. et anal. chim. appl., 1919, i, 294.

⁴ Ber. d. deutsch. chem. Ges., 1877, x, 796; 1878, xi, 235.

and shaken for about ten minutes. If the air contains carbon monoxid, a distinct pink color of the carbon monoxid hemoglobin will be noticed when the comparison is made with the original buff-colored blood.

Gas analysis apparatus of various types may be used for the analysis of larger quantities of carbon monoxid.¹ Hoover² recommends the use of Hoolunite (a mixture of fuming sulphuric acid, iodine pentoxid, and pumice stone) for the detection of carbon monoxide. This reagent gives a green color, varying in depth with the concentration of the carbon monoxid.

Hempel³ exposed mice to a contaminated atmosphere and examined their blood spectroscopically. By this means he was able to detect 0.5 per cent. of carbon monoxid, though his results are disputed by Gruber.

C. H. Wolf⁴ has also given directions concerning the detection of this gas. For poisonous quantities, especially in the air of mines and other closed places, use is made of its physiologic action. A cage containing several varieties of warm-blooded animals is hung in the suspected atmosphere; if they die and the blood shows the presence of carbon monoxid, the test is definite. White mice are preferable to gray, first because they are accustomed to captivity, and, second, because the color of the blood is clearly visible in the ears, nose, and eyes, the last being especially brilliant. Burrell⁵ claims that canaries are more sensitive to carbon monoxid, 0.2 per cent. causing distress in one and a half minutes, and they will fall from the perch in five minutes.

Detection of Carbon Monoxid in Blood.⁶—Since the discovery by Hoppe-Seyler in 1862 of the spectrum of oxyhemoglobin, and in 1864 and 1865 of the spectrum of carbon monoxid hemoglobin, and its irreducible character, no toxicologic analysis of the blood has been considered complete without this test being applied. In forensic medicine it was first applied in 1867.

Blood taken from persons or animals poisoned by carbon monoxid shows a characteristic absorption spectrum closely resembling that of oxyhemoglobin. The absorption occurs between the D and E lines chiefly, and is apparent through the appearance of two absorption bands of nearly equal intensity and width. The one near D coincides almost exactly with that of oxyhemoglobin of the same position; the space between it and the band toward F is considerably wider than that between the two bands of the oxyhemoglobin spectrum (see No. 7, Plate

¹ L. M. Denis, C. G. Edgar, *The Comparison of Rapid Methods for Determining Carbon Monoxid*, Jour. Amer. Chem. Soc., 1897, xix, 859.

² Jour. Ind. Eng. Chem., 1921, 13, 770. Kaleta, Th., *The Determination of Carbon Monoxid in Blast Furnaces by Combustion*, Chem. Ztg., 1922, 46, 430; Katz and Bloomfield, Jour. Ind. and Eng. Chem., 1922, 14, 304.

³ Zeitschr. f. anal. Chem., 1879, xviii, 399.

⁴ Pharm. Zeitschr., 1880, p. 268; Chem. Centralbl., 1880, 51, 773.

⁵ Technical Paper 11, Bureau of Mines, Washington, D. C., 1912; Burrell, Seibert and Robertson; Technical Paper 62, Bureau of Mines, Washington, D. C., 1914, p. 12.

⁶ The chemical detection of carbon monoxid in bodies embalmed with formaldehyd is limited largely to the tannin reaction (see p. 320), as the other reactions are obscured by the preservative. In this connection see Fishbein, Jour. Amer. Med. Assoc., 1913, 60, 737.

6). When more than 27 per cent. of the blood coloring-matter has been saturated by carbon monoxid, the addition to the blood of reducing agents, as a drop or two of a solution of crystallized ammonium sulphid, does not convert the spectrum into one of reduced hemoglobin. The character of this spectrum is that of a single band beginning on the D line and occupying a little more than half of the space to the E line (see No. 3, Plate 6). A solution of ferrous sulphate in ammonium tartrate may be substituted for the ammonium sulphid.¹

The spectroscopic examination may be made by the use of an ordinary spectroscope, or, in a more refined manner, especially on very small quantities of blood, with the microspectroscope. The single prism spectroscope has an adjustable slit which is provided with a micrometer set-screw so that a particular width of opening may be accurately determined. Two burners placed on an adjustable stand supply white light, the one directly to the spectroscope, the other

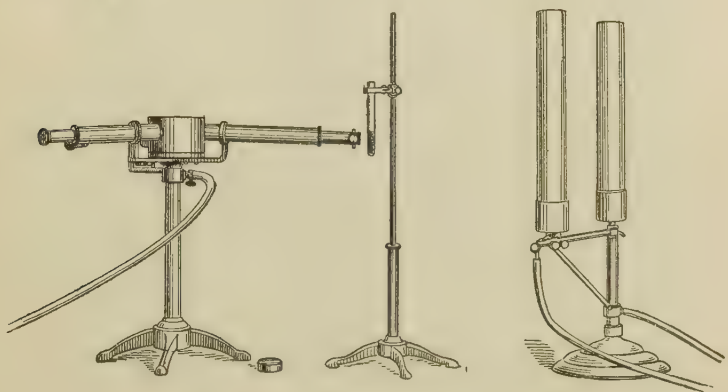


FIG. 40.—Spectroscopic examination of blood.

through a comparison prism attached to one-half of the slit. The blood contained in the test-tube is placed in the path of the rays from the first mentioned lamp. The lamps are provided with tin casings which allow the light to pass through small windows cut in them. The position of any absorption bands is determined by the illuminated scale of the spectroscope. Recently methods have been used whereby photographs of the blood spectrum may be taken with suitable precautions to exclude optical delusions.²

Dilution of the blood is advisable. Dreser³ has made use of this method for the quantitative determination of carbon monoxid in blood. About one-third of the hemoglobin of the blood remains unconverted into carbon monoxid hemoglobin at the time of death under the toxic action of this gas on man and animals. Since some claim

¹ Hoppe-Seyler, *Physiologische Chemie*, 1877, 384; *Med. chem. Untersuch.*, 1866, i, p. 202; W. Preyer, *Die Blutkrystalle*, Jena, 1871.

² G. Bider, *Arch. d. Pharm.*, 1892, cxxx, 609-640.

³ A. H. Dreser, *Arch. exp. Pharm.*, 1891, xxv, 119.

that carbon monoxid blood loses its characteristics when exposed to the air for a week, it is always advisable to seal up a specimen of the blood at the time of the autopsy. Such blood then retains its character for years.

Many prefer to extract the gas from the blood and measure and identify it. For this purpose 100 c.c. of the blood are introduced into

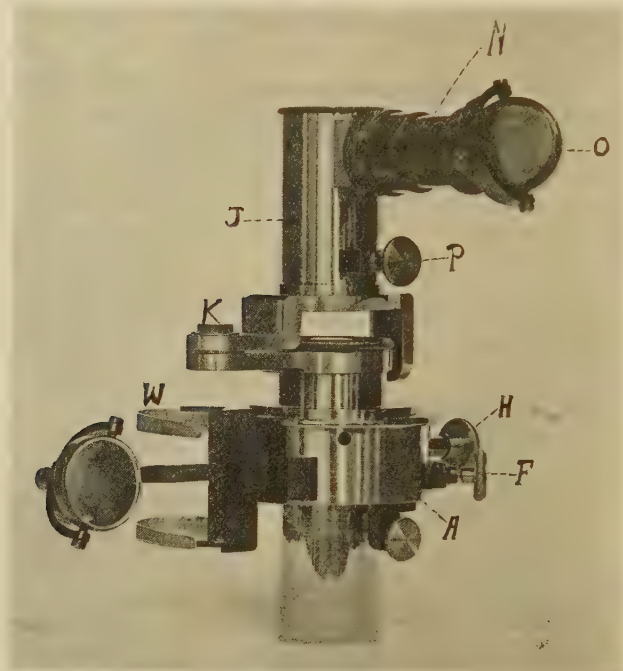


FIG. 41.—The microspectroscope. The instrument may be used for the detection of small quantities of blood in solution and is very useful in the detection of carbon monoxid hemoglobin. The instrument consists of two main divisions, the drum (A) which fits into the tube of the microscope and the spectroscope (J). The drum contains an adjustable slit worked by the screws (H) and (F) which controls the length and breadth of the ray of light which comes to the eye from the object. By means of the screws the spectra are properly focussed. The drum also contains a prism illuminated by a side mirror, and moved into or out of the field by a projecting lever. With this mirror is a clamp to hold a small tube of solution which it may be desired to test or which may be used to give a comparison spectrum. The spectroscope (J) revolves on the pivot (K), so that it can be brought into position over the eye-piece or moved away to permit focussing the object. At the side is a tube (N) which contains a scale, the divisions of which represent wave lengths, expressed in one hundred thousandths of a millimeter. By means of the mirror (O) the scale is thrown upon the spectrum of the object, and it is focussed by the sliding tube (N). It should be adjusted by the sliding screw (P) so that Fraunhofer's line (D), the sodium line, coincides with the division line 58.9, the wave length of the sodium line being 589 millionths of a millimeter. A small test-tube of known solution is placed in the clamps (W) at the side of the drum and compared with the unknown solution in a cell of 1 c.c. capacity, mounted on a glass slide on the stage of the microscope. The drum prism furnishes a comparison spectrum.

the spacious receiver of a mercurial air-pump. The extraction of the gas is begun by the exhaustion of the blood by the action of a solution of glacial acetic acid saturated with sodium chlorid and preferably boiled, and the application of heat to about 50° C. By the use of proper absorbents carbon dioxid and oxygen are removed, and the carbon monoxid can be measured by its absorption in cuprous chlorid solution. This solution may be caused to yield up its content of car-

bon monoxid by the addition to it of an excess of potassium hydroxid. The gas, if in sufficient quantity, may be ignited and seen to burn with a blue flame.¹

The apparatus shown in the illustration (Fig. 42), which is employed in the Toxicological Laboratory in Paris, may be advantageously used for extracting gases from blood. It consists of a container (a) of from 500 to 700 c.c. capacity, into which the blood is permitted to flow by means of the funnel (b) and stop-cock (c), the latter being large enough to allow clots to pass. Before the blood is let in the apparatus is exhausted by means of the mercury pump (d), aided by a water vacuum pump or by an air pump for quicker work. The gases disengaged from the blood are cooled in (e), dried by the strong sulphuric acid on beads in (f), deprived of carbon dioxid by stick

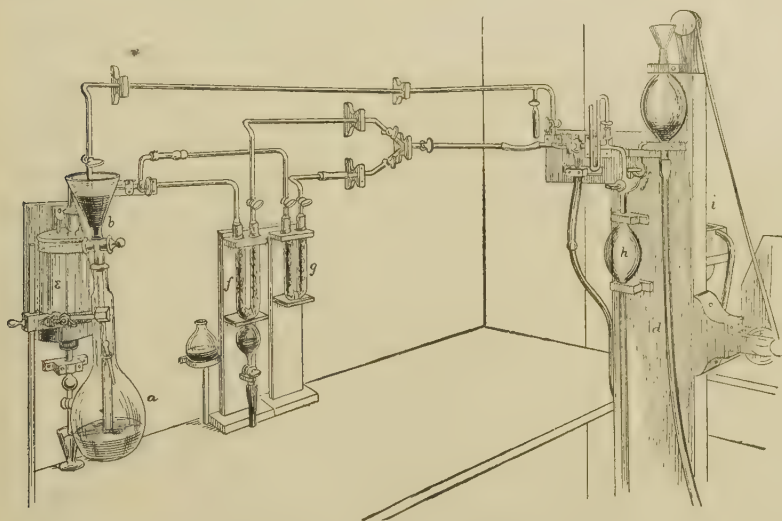


FIG. 42.—Apparatus for extracting gases from blood.

potassium hydroxid in (g), and finally carried to the holder (h). From this vessel they are delivered by aid of a capillary tube connected to the stop-cock (j) to a receptacle (not shown in the figure) placed in a pneumatic trough (i) holding mercury. The gases thus collected are then submitted to analysis.

The following additional tests are of importance because of their simplicity: Blood rich in carbon monoxid when boiled yields a brick-red mass; ordinary blood becomes brown-black (Hoppe-Seyler). Ten c.c. of 2 per cent. solution of a blood strongly charged with carbon monoxid, with 2 c.c. of yellow ammonium sulphid and 0.2 c.c. of 30 per cent. acetic acid, yields a bright red, while normal blood yields a green, precipitate (Katagama). When blood is added to diluted hydrogen sulphid water drop by drop, it produces a bright red precipitate

¹ Brouardel et Ogier, Documents sur les Travaux du Laboratoire de Toxicologie, Paris, 1891, p. 26.

when carbon monoxid is present, otherwise a bright green (Salkowski). Normal blood when shaken with one or two volumes of a solution of sodium hydroxid of 1.3 specific gravity becomes black, in thin layers dark greenish brown; carbon monoxid blood remains red and appears like red lead or cinnabar (Hoppe-Seyler). A mixture of calcium chlorid and sodium hydroxid produces a beautiful carmin-red color if carbon monoxid is present, while normal blood becomes brown (Eulenberg). A reducing agent, as ammonium sulphid, alkaline stannous chlorid solution, or a ferrous salt, changes the color of normal blood almost to black, while carbon monoxid blood retains its red color. Two c.c. of carbon monoxid blood with an equal quantity of water and 3 drops of a one-third saturated solution of copper sulphate when mixed produce a brick-red precipitate, while normal blood yields a greenish-brown one (Zaleski). When four or five volumes of lead acetate are added to one of carbon monoxid blood and thoroughly shaken for about a minute, it retains its red color; normal blood, under like circumstances, becomes dark. The differences increase by keeping, being visible for a week or two even in open test-tubes (Rubner). When 10 c.c. of blood are mixed with 15 c.c. of 20 per cent. potassium ferrocyanid solution and 2 c.c. of moderately strong acetic acid (one volume of glacial acetic acid to two volumes of water), a solid coagulum gradually results; if normal, the coagulum is black-brown, but when the blood contains carbon monoxid, bright red (Wetzel). Blood diluted 1 part to 4 with water and shaken with three times its volume of a 1 per cent. tannin solution becomes in twenty-four hours of a gray tint when normal, but is carmin-red when carbon monoxid is present. This color is still persistent in tubes that Doremus has kept for seven years. Paper moistened with a 2 : 1000 neutral solution of palladous chlorid, hung in a 10 liter bottle of air, will blacken if the air contains as small an amount as 0.05 part of carbon monoxid in 1000 parts of air. The paper is also blackened by hydrogen sulphid, ozone, and sulphurous acid. Some of the tests for detecting carbon monoxid in the atmosphere can be readily employed for detecting the gas when absorbed by the blood. Palladous chlorid can thus be made to indicate the presence and the quantity of carbon monoxid in blood.¹

Quantitative Methods.—*Haldane's² Quantitative Method.*—For the carbon monoxid, this yields satisfactory results with fresh blood, but with dark colored blood from cadavers, the colors are hard to match with a Dubosq colorimeter, the results obtained being far too high compared with the palladous chlorid method.

For the quantitative estimation of carbon monoxid in air and in blood, the *method of Nicloux³* or that of *Fodor⁴* is preferred to that of

¹ See Kohn-Abrest, *The Sanitary Analysis of Air Especially as Regards Carbon Monoxid*, *Chimie et Industrie*, 1919, 7, 590. Girard, R., *Recent Researches on Carbon Monoxid*, *Rev. Sci.*, 1922, 60, 195.

² Haldane, *Jour. Physiol.*, 1895, 18, 430, 463; 1896, 20, 521.

³ Nicloux, *Compt. rend. Acad. d. sc.*, 1898, 126, 746; *Bull. Soc. chim. biol.*, 1920, 2, 171; *Micromethod for Estimating Carbon Monoxid*, *Ibid.*, 1921, 3, 286.

⁴ Fodor, *Deutsch. Vrtljschr. f. off. Gesundheitspf.*, 1880, 12, 377.

Haldane, especially with blood from cadavers which may not be of a bright cherry red. The method of *Nicloux* is based on the action of the oxidation of carbon monoxid by iodic acid and the determination of the liberated iodine with a standard solution of thiosulphate. In a form of apparatus devised by Seidell,¹ the carbon dioxid liberated may also be determined. The reaction may be expressed by the equation: $\text{I}_2\text{O}_5 + 5\text{CO} = 5\text{CO}_2 + \text{I}_2$.

The *method of Fodor*, based on the reduction of palladous chlorid by carbon monoxid, is much better for the examination of carbon monoxid in blood. The reaction is expressed by the equation: $\text{PdCl}_2 + \text{CO} = \text{Pd} + 2\text{HCl} + \text{CO}_2$. For the examination of the blood, 5 c.c. are diluted with 20 c.c. of water in a large test-tube of 80 c.c. capacity; a small piece of sodium hydroxid is then added to aid in the expulsion of carbon monoxid. A tube containing 10 c.c. of palladous chlorid precedes the tube containing the blood to remove the carbon monoxid from the laboratory air. A third U tube following the tube containing the blood contains a solution of lead acetate, and a fourth tube contains dilute sulphuric acid. The chain of tubes is completed by the addition of three U tubes containing a solution of palladous chlorid.² The test-tube containing the blood is heated in a water-bath to 90° C., while a gentle current of air, previously drawn through the tube of palladous chlorid is conducted through the chain of tubes at the rate of 300 c.c. per hour for four hours. If carbon monoxid is present, the palladous chlorid is reduced, and a black precipitate of palladium will be deposited. The reduced palladium is collected on a filter-paper, washed with water, and dissolved in hot nitrohydrochloric acid. The U tubes after washing with water will have a small amount of palladium adhering to the sides. This can be dissolved in the hot nitrohydrochloric acid and added to that dissolved from the filter-paper. The solution is evaporated on the hot water-bath, taken up with strong hydrochloric acid three or four times to remove all traces of nitric acid. The residue is dissolved in water and titrated with a solution of potassium iodid containing 1.486 gm. to the liter. The diluted palladium chlorid solution is heated on the water-bath before each addition of the potassium iodid solution. A brown precipitate of palladous iodid is filtered off and the operation is repeated until the addition of potassium iodid fails to produce a brown cloudiness. Each cubic centimeter of the potassium iodid solution represents 0.1 c.c. of carbon monoxid. In case the blood contains only a small amount of carbon monoxid, as is demonstrated by the tannic acid and other color tests, 20 c.c. of the blood are used in a small Erlenmeyer flask. When it is desired to report the saturation of the blood after obtaining the percentage of carbon monoxid by volume, one can use the relation $x : 20$,

¹ Seidell, Jour. Indust. and Engin. Chem., 1914, 4, 321.

² The commercial salt is dissolved in hydrochloric acid, with the addition of nitric acid, evaporated to dryness on the water-bath, moistened with hydrochloric acid, dried, taken up with a small amount of water and again dried to free it from excess acid. The residue is then made up to volume so that 500 c.c. will contain 1 gm.

since a saturated blood will hold in combination 20 per cent. by volume of carbon monoxid.¹

Method of Van Slyke and Salvesen.—The principle of this method² is to set free the oxygen and carbon monoxid from their combination with hemoglobin in the blood by addition of ferrieyanid and then to remove both gases with the help of a Torricellian vacuum in the apparatus devised by Van Slyke for determining the CO₂ combining power of the plasma. The oxygen is absorbed in the apparatus by alkaline pyrogallate and the volume of residual carbon monoxid is measured directly at atmospheric pressure, a correction being made for the small and constant amount of nitrogen gas physically dissolved by the blood. From the recent work of O'Brien and Parker,³ who absorbed the carbon monoxid with a solution of ammoniacal cuprous chlorid and thus determined this gas directly, it is evident that the amount of CO dissolved in the blood-serum, used in the test, is so small that there is little to be gained by making a correction for this factor, as is done by Van Slyke in his method for oxygen of the blood and by Stadie for methemoglobin.

The blood-gas apparatus is prepared by introducing into it 5 drops of redistilled caprylic alcohol and 6 c.c. of ammonia solution made by diluting 4 c.c. of concentrated ammonia to a liter. If saponin powder is available, as much is added to the 6 c.c. of ammonia, while in the cup of the apparatus, as will stick to the end of a glass rod (approximately 1 mg. per c.c.). After the ammonia is introduced into the 5 c.c. chamber of the apparatus, the latter is evacuated and the air is extracted from the ammonia solution by shaking for about fifteen seconds. The extracted air is expelled, and the extraction repeated to make sure that no air is left in the solution. Finally, about 2 c.c. of the air-free ammonia are forced up into the cup of the apparatus. The oxalated blood is now thoroughly stirred with a rod to assure even distribution of the corpuscles, and a 2 c.c. sample is drawn into a pipet and run under the ammonia in the cup of the apparatus. (The lower delivery mark of the pipet should be 3 or 4 cm. above the tip, as a pipet calibrated for complete delivery would be inconvenient for placing the entire sample of blood below the layer of ammonia.) The blood is now run from the cup into the 50 c.c. chamber, the ammonia layer following the blood and washing it in. A few additional drops of the air-free ammonia may if necessary be added from a dropper to make the washing complete.

The blood and ammonia in the chamber are mixed and allowed to stand until the blood is *completely laked*. This requires about thirty seconds when saponin is present and five minutes when it is not. After

¹ See Florentin and Vandenberghe, *Compt. rend. Acad. des Sc.*, 1921, clxxii, 391; Nicloux, M., *Bull. soc. chim. biol.*, 1920, 2, 171; *Micromethod for Estimating Carbon Monoxid*, *Ibid.*, 1921, 3, 286.

² *Jour. Biol. Chem.*, 1919, xl, 103.

³ *Ibid.*, 1922, l, 289. See also Nicloux, *Bull. soc. chim. biol.*, 1919, i, 114; *Ibid.*, 1920, ii, 171; Hartridge, *Jour. Physiol.*, 1920, liii, lxxvii; Hill, *Biochem. Jour.*, 1921, xv, 577; Sayers and Yaut, *Jour. Amer. Med. Assoc.*, 1922, lxxviii, 1745.

laking is complete, 0.4 c.c. of a saturated potassium ferricyanid solution is introduced to set free the oxygen and carbon monoxid combined with the hemoglobin. (This ferricyanid solution is made by dissolving 40 grams of the salt in 100 c.c. of water and is made air-free by boiling or shaking in an evacuated flask and is kept in a buret under a layer of paraffin oil 2 or 3 cm. thick to exclude air.) The apparatus is now evacuated by lowering the leveling bulb until only a few drops of mercury remain above the lower stop-cock, and is shaken, preferably with a rotary motion, to whirl the blood in a thin layer around the wall of the chamber. If the blood was completely laked before the cyanid was added, extraction of the gases may be completed by half a minute of efficient shaking. The extracted solution may be drawn into the bulb of the apparatus below the lower cock and the extracted gas measured over mercury. When the reading of the volume of the gas mixture, consisting of oxygen, carbon monoxid, and a little nitrogen is constant, a solution of alkaline pyrogallate (prepared by dissolving 10 grams of pyrogalllic acid in 200 c.c. of strong potassium hydroxid, consisting of 160 grams KOH dissolved in 130 c.c. of water) is introduced into the cup of the apparatus, is covered by a thin layer of paraffin oil, and is allowed to flow slowly down into the inner wall of the graduated part of the apparatus. A little suction is produced during this part of the procedure by lowering the leveling bulb slightly. The absorption of the oxygen is quite rapid and is completed in less than one minute; the reading is taken and the pyrogallate solution introduced once more until a constant reading is obtained. The gas is then measured under the conditions of prevailing pressure and temperature. As the solution is very dark and it is a little difficult to get good readings of the meniscus, a new meniscus is produced by letting water flow down after the pyrogallate solution; the water floats on top of the fluid and one may obtain readings to about 0.002 c.c. The apparatus is washed out twice with dilute ammonia solution after each determination.

Calculation.—The gas measured is reduced to standard conditions by the use of the factor

$$X = \frac{B}{760} (100.8 - 0.27t) (V - 0.136 + 0.002t)$$

in which B equals the observed barometric pressure; t equals the observed temperature at which the analysis and readings were made; V represents the actual reading in mm., of the gas in the pipet, and X expresses the cubic centimeters of CO reduced to 0° C. temperature and 760 millimeter pressure.

If 2 c.c. of blood have been used, as directed in the test, the values of this factor may be found in the following table, the result then being expressed in cubic centimeters of CO per 100 c.c. of blood, from which amount the nitrogen correction, 1.2 c.c., is subtracted.

Temperature, C.	Factor by which observed gas volume is multiplied in order to give carbon monoxid in 100 c. c. of blood.
15°	$46.5 \times \frac{B}{760}$
16°	$46.3 \times \frac{B}{760}$
17°	$46.0 \times \frac{B}{760}$
18°	$45.8 \times \frac{B}{760}$
19°	$45.6 \times \frac{B}{760}$
20°	$45.4 \times \frac{B}{760}$
21°	$45.1 \times \frac{B}{760}$
22°	$44.9 \times \frac{B}{760}$
23°	$44.7 \times \frac{B}{760}$
24°	$44.4 \times \frac{B}{760}$
25°	$44.2 \times \frac{B}{760}$
26°	$44.0 \times \frac{B}{760}$
27°	$43.7 \times \frac{B}{760}$
28°	$43.5 \times \frac{B}{760}$
29°	$43.3 \times \frac{B}{760}$
30°	$43.1 \times \frac{B}{760}$

POISONOUS GASEOUS MIXTURES

Vapor from Burning Charcoal and Coal.—The three prominent factors in poisoning by products of combustion are diminution of oxygen, increase of carbon dioxid, and presence of carbon monoxid.

The vapors given off by the combustion of charcoal have been found to be highly poisonous, and though the carbon dioxid is in great proportion, the postmortem appearances and the symptoms indicate that the carbon monoxid is the more active agent.

From experiments by LeBlanc, a dog exposed to fumes of burning charcoal in a closed space succumbed when the air of the chamber contained carbon dioxid, 4.61 per cent.; carbon monoxid, 0.54 per cent.; carbureted hydrogen, 0.04 per cent.; oxygen, 19.19 per cent.; nitrogen, 75.62.¹ Biefel and Poleck have shown that charcoal fumes contain on an average a proportion of carbon dioxid to carbon monoxid of 20 to 1.²

¹ Taylor, Medical Jurisprudence, 12th Amer. ed., 1897, p. 469.

² Zeitschr. f. Biol., 1880, xvi, 279.

The use of coal leads to many fatalities, since an improperly constructed damper or an open stove-lid permits the products of combustion to escape into the living-rooms. This form of poisoning is by far the most common of all from gaseous poisons. Little warning is given in these cases, since, as a rule, there is but a small quantity of sulphur dioxid which, by its suffocating odor, would indicate the gas to the occupants of the rooms.

The system of heating dwellings used abroad leads to many accidental deaths from the fumes escaping from the braziers. This form of portable stove is also too frequently a ready means at hand for suicide, especially since in foreign countries the sale of drugs is so carefully regulated. The mortality in France¹ due to this form of gas poisoning far exceeds all other causes, and statistics from Germany² show that this handy means has proved the most popular. Medical jurists recognize, however, in these matters the influence of suggestion.³

Symptoms.—The symptoms are not unlike those already described for carbon monoxid. They have been described, indeed, by those who have succumbed to the action of the fumes—notably by Deal, who wrote of his sensations from the time of lighting the furnace at intervals of ten minutes until he became unconscious. A candle became extinguished, while a lamp continued to burn. The symptoms, from the beating of his temples to the madness that finally appeared, are all accurately described.⁴

The usual appearances of persons suffering from charcoal, coal, or coke fumes are: Lips purple; countenance livid; hands and nails purple; surface of body cold; breathing quick and short; pulse small, quick, and feeble; pupils fixed; total insensibility. There are cases, however, in which the face and skin are pale, eyes bright, and pupils dilated. There is often froth at the mouth or bleeding of nose or from lungs. Attitude generally composed; sometimes position shows an attempt to escape when overcome. There are sometimes contusions about head or body from precipitous falls. The bodies are, however, generally in a recumbent position, since most of the fatalities occur while the victims are asleep or have purposely assumed that position, having made preparation for self-destruction. When many are overcome, one or more may survive and show symptoms seemingly of drunkenness, or they are dazed, unable to answer questions, or, if able, answer incoherently; they are sometimes excited or delirious. These conditions frequently lead to a suspicion of murder, and there are many cases on record where the suspicions cast on the survivor have been dispelled only by a thorough investigation as to the cause of death. The fact that lamps, candles, or fires continue to burn is not evidence of the poisoning not being due to the products of combustion. At times the action of the vapors creeps on unawares.⁵ In one case the escape of a

¹ Hougounenq, *Toxicologie*, 1895.

² Lesser, *Atlas der ger. Med.*, 1883, i, 141.

³ Brouardel, *Les Asphyxies*, 1896.

⁴ Briand et Chaudé, *Manuel Complet de Médecine Légale*, Paris, 1858, p. 366.

⁵ Brouardel, *op. cit.*, p. 29.

large volume of furnace-gas from a defective flue into a church produced serious results. No one noticed the strong smell of gas. The congregation gradually became drowsy. During a lengthy closing prayer first one young woman and then another became unconscious. Others were made ill. The pastor became excited, and feeling strange sensations, called to the congregation to leave the church. All revived in the fresh air.¹

From the time of Orfila² the French medicolegists have studied the various phases of this type of poisoning, and their literature abounds in cases covering almost every conceivable complication of circumstances and their medicolegal bearings.

An elaborate series of experiments on animals under the influence of charcoal fumes and the result of the pathologic findings are given by Biefel and Poleck.³

Treatment should be the same as for poisoning by carbon monoxid alone.

Postmortem Appearances.—These vary considerably according as the asphyxiation occurs through a preponderance of one or the other of the poisonous constituents of the fumes, coinciding either with those already given for carbon dioxid or with those for carbon monoxid. Even under nearly similar conditions of poisoning the postmortem appearances may vary. A comparison of two cases where death resulted from fumes of burning charcoal is given by Taylor.⁴

Anders reports a case of a physician overcome; his servant dead. The symptoms, treatment, and postmortem findings are given.⁵

Vapors from Lime, Brick, and Cement Kilns.—These are closely allied in composition and effects to the fumes from burning charcoal, coal, or coke. They are, however, given out in such quantities that, when cooled on their exit from the kilns by the surrounding air, they float almost bodily in certain directions, there being insufficient time for their diffusion. It thus happens that people sleeping near by are overcome, or that, by a sudden change in the draft, workmen are prostrated as if they had descended into a pool of the gas. Here again the postmortem appearances⁶ incline either to those of carbon dioxid or monoxid, as already shown under the previous heading. Lime-kiln gases consist of carbon dioxid, 32 per cent.; carbon monoxid, 1.5 per cent.; oxygen, 1.5 per cent.; nitrogen, 65 per cent. Traces of sulphur dioxid and of hydrogen sulphid also occur if the fuel or charge contained sulphur.

It sometimes happens that, owing to the construction of the kilns, the gases are carried some distance underground before finding an exit.

¹ Daily journals, November 30, 1897. Also report, W. P. Mason, Jour. Amer. Chem. Soc., January, 1888, 10, 176.

² See Orfila, LeBlanc, Briand et Chaudé, Tardieu, Bugnion and De la Harpe, Devergie, Tourdes, Bernard, Brouardel, and others.

³ Biefel and Poleck, Ueber Kohlendunst, etc., Zeitschr. f. Biol., Munich, 1880, xvi, 279.

⁴ Medical Jurisprudence, 12th Amer. ed., 1897, pp. 469-471.

⁵ Defective Furnace Arrangements, Philadelphia Medical Times, 1880, v, 478.

⁶ D. Herman, Jour. Soc. Chem. Ind., 1896, xv, 857; also same, p. 856.

Their very variable composition may lead to the air being suddenly contaminated.

A practical and very instructive illustration of poisoning from these gases presented itself in 1887, at Malaunay, in the neighborhood of Rouen, where a certain Druaux kept a wine-shop in close proximity to a lime-kiln. Druaux and his wife's brother were found dead in the house, and Madame Druaux in a state of supposed intoxication. She was unable or unwilling to give any account of what had happened or any explanation of the fatalities, and was at once suspected of having administered poison. She was tried and found guilty. Her attorney was convinced of her innocence, and more by threats than by persuasion he succeeded in having her set at liberty after an incarceration of five years and nine months. Subsequently the matter was brought before the Court of Assize at Amiens, when the evidence then produced distinctly proved that carbon monoxid from the lime-kiln was not only the cause of the death of her husband and brother, but also of her supposed intoxication at the time. She was formally declared innocent, and awarded 40,000 francs as compensation for false imprisonment.

"After-damp" and Gases Left After Explosions of Gun-powder, Gun-cotton, etc., in Mines.—These also resemble the products of combustion already given. According to Haldane, after-damp consists of nitrogen and argon, 88.3 per cent.; carbon dioxid, 11.7 per cent.; while the gaseous mixture left along the track of explosions in coal-pits is carbon dioxid, 5 per cent.; carbon monoxid, 1.25 per cent.; oxygen, 12.5 per cent.; nitrogen and argon, 81.25 per cent. The argon is in the proportion of 1.18 in 100 volumes of mixed nitrogen and argon.¹ When sulphur gun-powder is used, sulphur and cyanogen compounds also result, while with nitro-powders, oxids of nitrogen are readily detected. Full details of appearances, symptoms, and pathologic findings are given in the voluminous special literature of mines, mining, and explosives.

"Water-gas," "Producer Gas," "Fuel Gas."—These technical names have been given to mixtures of combustible gases manufactured for general distribution or for special use in chemical and metallurgic works.

When steam is passed through red-hot coke, carbon monoxid and hydrogen should theoretically result; practically carried out, the process also yields carbon dioxid and marsh-gas. The resulting gas is odorless and very inflammable. When air is added, it forms a highly explosive mixture. Analyses of such gases are given by Herman.²

The great danger in the use of this gas by the public lies in its odorless character, its escape into the air remaining undetected; numerous casualties have resulted in which the histories disclose the fact that people were suddenly overcome while busy with the routine work of the house or trade.

The manufacture has been largely discontinued or modified to avoid

¹ Th. Schloesing, Jr., *Comptes Rendus*, 1896, cxxiii, 302.

² *Jour. Soc. Chem. Ind.*, 1896, xv, 857.

these defects. In Europe the sale of such gas is interdicted. The better methods of gas-fitting practised in this country have lessened the fatalities.

A fierce discussion has brought out many facts regarding the use of these gases, all of which are to be found in technical literature and official reports.^{1, 2, 3}

Symptoms, treatment, and postmortem condition are practically the same as in poisoning by carbon monoxid (see p. 307 et seq.). A few cases are selected from the numerous ones on record:

Two forge men, occupying a cabin where there was a cooking gas-stove supplied by water-gas, in the course of the day were found dead, as if asleep. The gas-cock was partially turned on. At the autopsy, two days later, the bodies were examined by several medical men. Before the bodies were well opened the gas that escaped from them into the air of the room, of 39,000 cubic feet capacity and receiving 1000 cubic feet of fresh air a minute, was so contaminated as to affect several—one seriously—but all recovered.⁴ The viscera presented the appearances of carbon monoxid poisoning, and the blood and viscera kept in stoppered bottles showed a rosy hue seventeen months later.

On January 6, 1887, owing to a break in the street mains in the city of Troy, N. Y., a quantity of fuel-gas passed beneath the frozen crust of earth and found its way into the adjoining houses. Three deaths and many more or less serious cases of illness resulted. The gas contained carbon dioxid, 5 per cent.; carbon monoxid, 37.5 per cent.; hydrogen, 48 per cent.; nitrogen, 7.1 per cent.; oxygen, 0.5 per cent.; marsh-gas, 0.9 per cent. The expressions of the deceased were placid. One victim, an old woman, was found seated in a chair holding her false teeth in her hand. The second, also a woman, lay upon the floor. The third, a man, sat upright on a lounge, his head reclining on his shoulder. The fire was burning in the stove, and the lamps were still burning on the table. Rigor mortis was fully developed. Upon opening the cavity of the chest of one of the victims the physician bent forward and took one or two long whiffs for the purpose of detecting the presence of any odor. Almost immediately he was seized with giddiness and great oppression in the epigastrium, and was obliged to discontinue work for half an hour. The effects did not finally wear off until after twelve hours. Appearances of the organs were those of carbon monoxid poisoning. A bottle of blood taken from the heart at the time of the autopsy was examined in February, 1888. The bottle had been closed with a tight cork. The blood had a strong odor of putrefaction, and was of a brilliant, vivid-red, the same as noted at the autopsy. A few corpuscles were visible with the microscope. Characteristic absorption

¹ S. W. Abbott, *The Relation of Illuminating Gas to Public Health*.

² W. T. Sedgwick and W. R. Nichols, *A Study of the Relative Poisonous Effects of Coal- and Water-gas*, Sixth Annual Report Mass. State Board of Health, Boston, 1885.

³ Tenth Annual Report, Board of Gas and Electric Light Commissioners of Mass., Boston, 1895.

⁴ Taylor, *Medical Jurisprudence*, 12th Amer. ed., 1897, p. 479.

bands were obtained with the spectroscope. The blood retained its character nearly two years from the date of the autopsy.¹

In another case a father and 2 children were all taken sick right after dinner. When a physician came, he found that the father and 1 child had vomited freely. The child was drowsy, cold, and almost insensible. The father's head was cold, with perspiration on forehead. The other child was faint. The mother was sitting up, hands rigidly outstretched, able to talk, but at moments losing consciousness. All recovered by fresh-air treatment. They used a large fuel-gas stove, and it was found that it had been turned on and not lit—for how long is not stated. The fuel gas was made from anthracite coal and had a very slight odor.²

SATURATED HYDROCARBONS

METHANE

(Chemical formula, CH_4 = 16. Synonyms, "Marsh-gas"; "Light Carburetted Hydrogen"; "Fire-damp")

This gas is a natural product forming the major portion of "natural gas" and the "fire-damp" of the mines. According to the report of the United States Geological Survey, there were 40,369 wells producing natural gas December 31, 1918. West Virginia had 9687 wells; Oklahoma, 1598; Pennsylvania, 15,244; Ohio, 6168, enumerated in the order of greatest production.³

The uses of the gas are chiefly domestic fires and lighting by mantle systems, iron works, and glass works. "Fire-damp" is ever present in certain mines. In the Wilkesbarre anthracite region there is a constant outflow of gas that is piped to the surface and burns the year round. Accidents are frequent, and visitors are dissuaded from entering the mines. The gas mixes readily with air, owing to its lightness (specific gravity, 0.5596), and forms an explosive mixture as soon as it amounts to one-eighteenth of the volume of the air. Fortunately, the mixture does not ignite readily. Electrolytic gas—hydrogen and oxygen—ignites at 674° C.; marsh-gas and oxygen, at 656° C.^{4, 5, 6} The force of explosion of the latter is 557 pounds per square inch, while marsh-gas with air gives 210 pounds per square inch. The miner's safety-lamp indicates by the "corpse light," or faint blue flame extending in the gauze cylinder, the presence of the gas before the proportion has reached the explosive stage.

As the gas has no odor, the miner is never warned of its presence by the sense of smell. It is only slightly soluble in water. It burns with a pale, illuminating, smokeless flame. In burning it yields watery

¹ W. P. Mason, Fatal Poisoning by Carbon Monoxid, Jour. Amer. Chem. Soc., 1886, x, 176.

² R. N. Flagg, San. Eng., New York, 1882, v, 39.

³ Mineral Resources of the United States, Dept. of the Interior, Geological Survey, 1918, pt. 2, 1393.

⁴ Victor Meyer, Berichte d. deutsch. chem. Ges., 1893, xxii, 428.

⁵ Freyer and V. Meyer, Zeitschr. f. phys. Chem., 1893, xi, 28.

⁶ A. Mitscherlich, Berichte d. deutsch. chem. Ges., 1893, xxvi, 160; xxvi, 428.

vapor and carbon dioxid—"after-damp." It forms a large proportion of illuminating gas, and is present in "water-gas," "producer gas," etc.

Though generally considered an indifferent¹ gas, it has slight toxic properties. When mixed with air, it greatly reduces the proportion of oxygen; 45 per cent. marsh-gas with air leaves 11.5 per cent. oxygen and 43.5 per cent. nitrogen, while 70 per cent. reduces the oxygen to 6.3 per cent. and the nitrogen to 23.7 per cent. Haldane's experiments may be briefly put in tabular form and be thus compared with other gaseous mixtures:

CARBON MONOXID (CO).		CARBON DIOXID (CO ₂).		FIRE-DAMP OR ME- THANE (CH ₄).		OXYGEN (O).	
Percentage present in air.	Effects on man.	Percentage present in air.	Effects on man.	Percentage present in air.	Effects on man.	Percentage present, remainder being N.	Effects on man.
0.05	After half an hour or more, giddiness on exertion.	3.5	Breathing deeper.	5.5	Nil.	17.3	Nil.
		6.0	Marked panting.	45.0	Breathing slightly deeper.	12.0	Breathing slightly deeper.
0.1	After half an hour or more, inability to walk.	10.0	Severe distress.	70.0	Life endangered.	9.0	Breathing deeper and more frequent.
		15.0	Partial loss of consciousness.				Face bluish.
0.2	After half an hour or more, loss of consciousness and perhaps death.	25.0	Final death.			5.0	Loss of consciousness and final death.
						0.0	Death with convulsions.
1.0	After a few minutes, loss of consciousness and final death.						

While toxicologically it has little interest, from the fearful loss of life it annually causes through explosions in mines and as the result of escaping street gas it has a very important forensic bearing.

The extensive experiments relative to explosions in mines are closely related to the numerous explosions that have occurred in various cities since the introduction of steam heating and electric lighting, explosions that have resulted in the loss of many lives and of much property. Among these may be mentioned the serious one that took place some time since in Boston, where, during the construction of the underground road, a leak occurred followed by a disastrous explosion, causing extensive wreckage and great loss of life.

In the experiments of Mason and Wheeler² on the propagation of the

¹ L. Hermann, *Lehr. der exp. Toxikologie*, Berlin, 1874, p. 275.

² *Jour. Chem. Soc.*, London, 1920, 117, 36.

flame in mixtures of methane and air, a speed of the flame was about 60 m. per sec. and was of short duration.¹

The higher homologues of this series, C_nH_{2n+2} , are to be found in petroleum and are collected in the first distillates when cooled to a sufficiently low temperature. Other still higher members occur, as gasoline, naphtha, etc. They have highly anesthetic properties, and have been used for such. Recently boys were detected in Philadelphia who climbed the lamp-posts, dipped rags in the naphtha of the reservoirs, and inhaled the vapors. They became mildly intoxicated. The effect was similar to that of liquor taken internally.²

UNSATURATED HYDROCARBONS

ACETYLÉNE

(Chemical formula, $C_2H_2 = 26$)

This gas, present in very small proportion in illuminating and in oil gas, has recently acquired importance through the manufacture of calcium carbide by the aid of the electric furnace by the Willson process.³ When wetted with water, calcium carbide changes to slaked lime and evolves acetylene. This ignites readily and burns with a brilliant but smoky flame. When burned from a properly constructed jet, it gives a very white light of greater intensity than any other known gas. A brilliant display was made of this at the Pan-American Exposition at Buffalo in 1901.

Acetylene is an endothermic compound. When a little fulminate of mercury is exploded in it, it detonates with violence, being decomposed into carbon and hydrogen (Berthelot). Mixed with a proper proportion of oxygen and ignited in an open mortar, it shatters the vessel (Victor Meyer). Mixed with air it also forms a violent explosive. Cyanogen compounds are formed as the result. It unites with metals, forming acetylides, that of copper being the best known. These are also explosive. Acetylene may be liquefied at 0° C. under 26.05 atmospheres pressure. It is said to be the lightest liquid known, and has a high coefficient of expansion. This liquid is considered more explosive than the gas. In some countries liquid acetylene is classed as an explosive.

The gas has an odor of geranium, and is agreeable when pure (Moissan). Its escape into the air is usually detected because of the impurities. It is a product of all incomplete combustions of hydrocarbons, and is, therefore, found when lamps or gas-jets are allowed to burn with an insufficient air-supply. The characteristic odor of a Bunsen burner

¹ Payman, Jour. Chem. Soc., 1920 117, 48. Wheeler, Jour. Chem. Soc., 1920, 117, 903. Ignition by Impulsive Electrical Discharge Mixtures of Methane and Air. Smith and Hamon, Methane Accumulation from Interrupted Ventilation, U. S. Bureau of Mines, Tech. Paper, 1918, 190, 46—1 or 2 per cent. of Methane in Mine Air Increases Decidedly the Liability to Propagation of Air Explosure. Seibert and Harpster, Use of the Interferometer in Gas Analysis, U. S. Bureau of Mines, Tech. Paper, 1918, 185.

² Amer. Gas-light Jour., 1897, lxvii, 774.

³ Rosemann, The Mineral Industry; A. H. Cowles, 1898, p. 75 et seq.; also Frank and Weil.

which has "retreated" or of an oil- or gas-stove-heated room is due mainly to acetylene.

It is also an intermediate product in the combustion of olefiant gas, and it escapes unburnt in the use of illuminating gas (Lewes). It is absorbed by water in sufficient quantity to impart a strong smell to the water and to yield precipitates with either ammoniacal cuprous chlorid or silver nitrate.

Very little was known of its physiologic action until recently, when experiments with large quantities showed that a considerable amount may be present in air without causing ill effects.¹

Dogs can inhale 20 per cent. pure acetylene for one hour without any other apparent supply of air; 40 per cent. caused stupor, coma, vomiting, and deep low breathing. The impurities of the gas are the chief causes of the toxicity. In the manufacture of acetylene gas from calcium carbide and water it usually contains hydrogen sulphid, phosphin² 0.04 per cent., and carbon dioxid, carbon monoxid 0.5 per cent., carbon disulphid 0.5 per cent. If carbon disulphid were present in abnormally large amounts, then the sulphur dioxid by combustion would be irritating to the mucous membrane. In 2 cases of poisoning³ the patients were in a deep comatose condition, associated with slow breathing, vomiting, cyanotic face, small, fast and irregular pulse, wide and expressionless pupils. After inhalation of oxygen both men improved. One patient after an hour became very restless, had hallucinations, waved arms, and sometimes would burst into hard laughter. Both men in two hours fell into a deep sleep. Upon awakening, dizziness, headaches, restlessness and a depressed feeling were noted, which disappeared in several hours.⁴

The combination⁵ with hemoglobin claimed to take place, as with carbon monoxid and with nitric oxid, to form a bright red compound which becomes gas free by the action of reducing agents, is denied by recent observers.

From experiments upon blood acetylene has been found to behave as an indifferent gas.⁶

Tests.—Acetylene may be estimated in illuminating gas and in air mixtures⁷ by means of Ilosva's reagent⁸ which gives an immediate red precipitate of copper acetylid, upon shaking the solution with a portion of the confined gas.⁹ Fill a 3 liter separatory funnel with illuminating

¹ N. Grehant, Sur la toxicité de l'acetylene, *Comptes Rendus*, 1895, cxxi, 564; L. Brociner, *Ibid.*, 1895, cxxi, 774.

² Pontoppidan (*Ugesk. f. Laeger.*, 1921, 83, 1222) reports a case of poisoning from acetylene, in which the symptoms indicated phosphoreted hydrogen poisoning. Acetylene gas not infrequently contains sufficient of this impurity to cause toxic effects.

³ Nicol, *Müncher Med. Wehnschr.* 1916, 63, 193.
⁴ Bettink, *Utrecht Pharm. Weekblad*, 1917, 54, 513, Acetylene and Its Toxicologic Effects.

⁵ Liebreich and Bristow, *Ber. d. deutsch. chem. Ges.*, 1868, i, 220.

⁶ L. Hermann, *Lehrbuch der exp. Toxikologie*, Berlin, 1874, p. 115.

⁷ Arnold, Molleny, Zimmerman, *Ber. d. Chem. Ges.*, 1920, 53, 1034.

⁸ *Ber. d. Chem. Ges.*, 1899, 32, 2698.

⁹ This reagent is prepared by dissolving 1 gm. of cupric nitrate ($\text{Cu}(\text{NO}_3)_2 \cdot 5\text{H}_2\text{O}$) in a 50 c.c. flask with a little water, adding 4 c.c. of ammonium hydrate and then 3 gm. of hydroxylamin hydrochlorid and making the mixture up to 50 c.c. with water.

gas; place about 20 c.c. of the reagent in the funnel and shake frequently during one hour. Transfer to a beaker and dilute with ammonia-water to prevent air oxidation; filter and wash well. Place the precipitate with the filter in a crucible with a little concentrated nitric acid, heat, weigh the copper oxid. The calculation assumes that $(\text{Cu}_2\text{C}_2\text{H}_2)\text{O}$ is formed.

$$\begin{aligned} X &= 100 \text{ g. } (1 + 0.00366t) 107/\text{vp.}, \text{ in which} \\ X &= \text{per cent. } \text{C}_2\text{H}_2, V = \text{vol.}, p. = \text{barometric pressure} \\ t &= \text{temperature and g. is the weight of the CuO.} \end{aligned}$$

Willstätter and Maschmann¹ filter the copper salt obtained as above on a long fibered asbestos suction filter, and wash to remove excess of ammonia. When wash-water remains pink on the addition of 1 drop of 0.1 normal KMnO_4 , the precipitate is dissolved on the filter with 25 c.c. of acidified ferric sulphate (100 gm. ferric sulphate, 200 gm. H_2SO_4 , make up to 1 liter). The filtrate is titrated with N/10 KMnO_4 according to the equation: $\text{C}_2\text{Cu}_2 + \text{Fe}_2(\text{SO}_4)_3 + \text{H}_2\text{SO}_4 = 2\text{FeSO}_4 + 2\text{CuSO}_4 + \text{C}_2\text{H}_2$.²

ETHYLENE

(Chemical formula, $\text{C}_2\text{H}_4 = 28$. Synonyms, *Olefiant Gas; Heavy Carbureted Hydrogen*)

This is a constant constituent of gas obtained by the destructive distillation of wood, coal, or oils. The "illuminants" of ordinary illuminating gas consist of a mixture of ethylene, propylene, and higher homologues, with which are also mixed members of other series, as benzene, naphthalene, etc. It has a pleasant odor, is slightly soluble in water, and unites directly with chlorine or bromine. The action of this gas and also of the other gases of this group is that of a weak narcotic. Gases of this category are now made by the destructive distillation of oil, and are then compressed in iron cylinders. These supply the gas for the Pintsch system of lighting.

Harvey³ uses castor oil plants to detect ethylene in the air, claiming that in air atmosphere containing as little as 0.00001 per cent. C_2H_4 will cause the petioles of the leaves to drop or the lamina to fold down. The gas is also said to be poisonous to sweet pea seedlings and carnations.

Beyond their narcotic action the other gases of this group have slight interest here.⁴

ILLUMINATING GAS

This is a mixture of various combustible gases, only certain of which, the "illuminants," burn with a bright, nearly white flame. The greater portion of the gas is hydrogen, with methane next in quantity. As the methods of manufacture differ and are continually

¹ Ber. der d. chem. Ges., 1920, 53, 939.

² Muller, Bull. Soc. Chem., 1920, 27, 69.

³ Jour. Roy. Hort. Soc., 1914, 40, 300.

⁴ Mahsoff and Egloff, A Review of the Chemical and Physical Properties of Ethylene, Jour. Physiol. Chem., 1919, 23, 65.

changing, it is difficult to give an average analysis. Four or five varieties are delivered to consumers in New York. In Chicago two grades of gas are distributed—on the North and Northwest Sides straight water-gas, and on the South Side a mixture of two-thirds water-gas and one-third coal-gas. All observers agree, however, in ascribing its poisonous properties to the carbon monoxid it contains. Street gas deprived of carbon monoxid is not destructive to mice, though 11 per cent. be present in air (Gruber) and the air breathed for hours. Though stupefied, they recover promptly. Animals live in marsh-gas or hydrogen if supplied with sufficient oxygen (Freitag). Fortunately, the intense odor of street gas enables it to be detected long before the proportion of carbon monoxid in the air reaches the toxic limit. Tidy claims 1 part in 12,000 of air—certainly 1 in 8000; Soyka, 0.01 to 0.02 per cent., when the carbon monoxid would be only 0.004 per cent; Gruber and others give the toxic limit of carbon monoxid as 0.02 per cent. The volume of gas lost to manufacturers by leakage is large—generally not far from 10 per cent.¹

The retentive power of the soil on the odoriferous constituents of gas was accurately demonstrated in a long series of experiments, and many investigations bearing upon the subject of the escape of gas into dwellings through the soil were made by the workers in Pettenkofer's laboratory.²

An exhaustive experimental investigation concerning the permeation of the soil by gases showed that the ventilation *toward* dwellings was greater in winter than in summer, and the liability to poisoning in correspondence thereto.³

Cobelli gives the details of a case where the mother and two daughters were fatally poisoned.⁴

A father, mother, and daughter were overcome in Berlin, by gas leaking from a pipe a distance of 30 to 35 meters.⁵ A similar case is given by Wolffberg.⁶

Numerous experiments and many observations in cases of death from this kind of poisoning show that the toxic atmosphere may contain an insufficient quantity of gas to form an explosive mixture. It needs one volume of gas to twelve of air to explode. In greater proportion, as one to four, there is no explosion, but the gas takes fire.⁷

¹ Th. Weyl, *Hyg. der chem. Gross-Indus*, Jena, 1896.

² Max von Pettenkofer, *Populäre Vorträge*, 1877, pt. i, pp. 89-92; Biefel and Poleck, *Ueber Kohlendunst und Leuchtgasvergiftung*, *Zeitschr. f. Biol.*, 1880, xvi, 312-315.

³ Welitschokowsky, *Experimentelle Untersuchungen ueber die Verbreitung des Leuchtgases und des Kohlenoxids im Erdboden*, *Arch. f. Hyg.*, 1883, i, 210; A. Suderkoff, *Ueber die Bewegung des Leuchtgases im Boden in der Richtung von geheizten Wohnräumen*, *Ibid.*, 1886, v, 166.

⁴ Cobelli, *Vergiftung der Familie Caini durch Leuchtgas*, *Zeitschr. f. Biol.*, 1876, xii, 420-433.

⁵ Jacobs, *Berlin klin. Wochenschr.*, 1874, 11, 322.

⁶ *Leuchtgasvergiftung nach Bruch des Strassenrohres*, *Arch. f. Hyg.*, 1883, i, 265.

⁷ Biefel and Poleck, *op. cit.*; Sonnenschein, *Handb. der ger. Med.*, 1869, p. 296; Dr. Schutt, *Vierteljahresschr. der ger. Med.*, third series, 1896, vii, 162.

Street gas deprived of odor has poisonous properties nearly like those of water-gas or charcoal fumes. Indeed, a differential diagnosis between poisoning by illuminating gas and that by charcoal fumes is difficult to establish, even if the blood shows the characteristic carbon monoxid hemoglobin spectrum. This, however, has been attempted.¹ When symptoms of carbon monoxid are present in marked degree, illuminating gas is indicated. Sooty appearance of the mouth and nostrils tends to show charcoal fumes. Circumstantial evidence is more valuable than the pathologic appearances. Comparative experiments on animals are given by Biefel and Poleck.² It is difficult to diagnose a case of gas poisoning from one by alcohol or opium.³ The character of the urine should be determined. It is often suppressed; sometimes albuminous; urea is sometimes absent.⁴

Symptoms.—Usually giddiness and headache, vomiting, loss of memory, unconsciousness, convulsions, and loss of muscular power, and finally complete asphyxia. Liebmann⁵ reports a case of severe interstitial and parenchymatous myocarditis from poisoning with illuminating gas. Zondek⁶ shows that in rabbits, illuminating gas produces a cardiac dilatation, analagous to that observed in man, persisting for twenty to thirty hours. Laignel-Lavastine and Alajouanine⁷ record the occurrence of gangrene of the foot following severe poisoning with illuminating gas.

As the number of cases, usually accidental or suicidal, is now very great, only a few can be referred to. One having a legal bearing of importance has been kindly communicated by Professor E. H. Bartley:

"A workman in a gas-house was found dead at the bottom of a well in the gas-house where he worked. He was in the habit of going into this well as a part of his regular duties, going down a ladder. After his death it was claimed that on this day there was a leak in the pipes in the well, so that it was so full of gas that when he attempted to go down the ladder he was overcome by the gas, causing him to fall to the bottom, where he died of suffocation. On the other hand, the gas company claimed that there was no unusual leak in the pipes on that day, and that the man fell as the result of his carelessness or as a pure accident, and that his death was caused by concussion of the brain. The blood had a peculiar red color, and about 2 ounces of it were examined. Chemical and spectroscopic examination showed the blood to be thoroughly saturated with carbon monoxid. It retained its bright color for many days. From this fact it was concluded that the man had really died from gas-poisoning, and not from concussion of the brain or suffocation."

¹ J. Deichstetter, *Die gerichtlich-medicinische Differentialdiagnose zwischen Leuchtgas- und Kohlendunst-Vergiftung*, Friedreich's Blätter f. ger. Med., 1896, lxxiv, 35.

² Biefel and Poleck, *Ztschr. f. Biol.*, 1880, xvi, 312.

³ John Norris, *Maryland Med. Jour.*, 1880-81, vii, 341.

⁴ McVey, *Medico-Legal Journal*, 1897, xv, 270.

⁵ *Deutsch. med. Wehnschr.*, 1919, xlv, 1192.

⁶ *Ibid.*, 1920, xlv, 235.

⁷ *Bull. de Soc. de Méd. des Hôp. de Paris*, 1921, xlv, 484.

Treatment.—According to methods given under Carbon Monoxid.
Postmortem Appearances.—(Same as Carbon Monoxid.¹)

HYDROGEN SULPHID

(Chemical formula, H_2S = 34. Synonym, *Sulphuretted Hydrogen*)

This colorless, transparent gas, possessing the smell of rotten eggs, is found naturally in volcanic regions and impregnating many spring-waters. It is quite soluble in water, that of mean temperature dissolving 3.23 times its bulk of the gas. It is a product of the putrefaction of organic substances containing sulphur, and therefore always found where vegetable or animal matter is undergoing decay, as in cesspools, sewers,² privy vaults, and tannery vats.³ It is also generated by the decomposition of organic matter by anaërobic bacteria in deep lakes and ponds, tainting the water or coming to the surface and tainting the atmosphere, where its presence is indicated by the discoloration caused to dwellings painted with white lead. Many of the small estuaries receiving the sewage of towns become defiled with this gas, being little more than open sewers. From such sources the gas is frequently discharged in considerable quantities, and is carried by the shifting winds in different directions. It is formed spontaneously whenever a soluble sulphate remains in contact with decaying organic matter with deficiency of air; directly by the union of sulphur and hydrogen; indirectly by the action of acids on the sulphids of the metals, generally ferrous sulphid; in certain mines found occasionally as an occluded gas in coal seams or places where there is decomposition in the presence of water.⁴ It is usual to prepare it in the laboratory from such sources as the latter. The gas is rarely pure. It is set free when sulphur is heated with damp wood, charcoal, tallow, or paraffin-wax. Its intense odor enables it to be recognized when present in minute quantities, 1 part in 10,000 being easily noted. It is slightly heavier than the air—specific gravity, 1.1912.

The solution in water gradually changes, depositing white sulphur. The gas is decomposed by heat into its elements. It is combustible, burns with a blue flame, producing water and sulphur dioxide, or, if the air is limited, some sulphur is deposited. It is decomposed in the presence of moisture by sulphur dioxide.

It explodes when mixed with half its volume of oxygen and ignited, with a deposition of sulphur; but two volumes of hydrogen sulphid and three of oxygen yield sulphur dioxide on explosion. It is one of the

¹ Kobert: Intoxikationen, Stuttgart, 1906, ii, 865. Koppel, Inaug. Dis., Dorpat, 1891, pp. 120-136. Maschka, Handb. der ger. Med., Prag and Tübingen, 1882, p. 338. Casper-Liman, Handb. der ger. Med., Berlin, 1889, ii, pp. 604-637, 8th ed. Woodman and Tidy, Forensic Medicine and Toxicology, Philadelphia, 1887, pp. 486-488. Müller, Vrtljschr. f. ger. med., 1921, 61, 1.

² Klein, W., Ueber die Vergiftung durch Einatmen von Kloakengas, Deutsch. ztschr. f. d. ges. gerichtl. Med., 1922, 1, 228.

³ Tauss, Zentralblatt f. Gewerbehyg. 1920, 8, 74; see also Myers, Jour. Bacteriol., 1920, v, 231.

⁴ Kober, G. M., and Hanson, W. C., Diseases of Occupation and Vocational Hygiene, Philadelphia, P. Blakiston's Son & Co., pp. 47, 620.

products of putrefactive processes in the body, especially in the intestine, and leads to auto-intoxication, Wells¹ asserting that as much as 66 mg. may be present in each 100 grams of normal colon contents.

Symptoms.—Breathed in its pure state this gas is immediately fatal. It acts upon all animals through all tissues, especially the lungs. If somewhat diluted it produces nausea, giddiness, cold skin, labored breathing, irregular action of the heart, transient auricular fibrillation as noted in one case,² pains in the stomach, and death by coma or in violent convulsions, with tetanus and even delirium. In greater dilution sleepiness will be produced, the continued respiration of the gas proving fatal, sensibility not being restored. In exceedingly dilute condition it sometimes occasions febrile symptoms somewhat resembling typhoid. Air containing 0.05 per cent. was the limit that men could breathe (Lehman); 0.02 to 0.075 per cent. produced no effect on a 12½ pound dog, 0.15 per cent. caused unconsciousness in a short time. Haldane considers 0.07 per cent. sufficient to cause death if breathed for some time. Headaches and dizziness may follow after twenty-four hours.³ Sometimes symptoms appear after a considerable lapse of time after breathing the gas, and they may continue for some days. Sugar and urobilin have been found in the urine. Sodium sulphid (2 mg. per kilo) when injected intravenously liberates hydrogen sulphid in the blood and induces hyperpnea followed by apnea vera.⁴

Chronic Poisoning.—Animals, as rabbits, exposed to the gas or mice living in sewers appear to become more or less habituated, and the same is true of men. Workmen in daily contact with the gas develop conjunctivitis, headache, and permanent gastric disturbances. The countenance becomes pale. The skin has a tendency to become furunculous. Chemists who frequently work with hydrogen sulphid are troubled with nervous headache in later years, and become exceedingly sensitive to this gas, which was at former times not unpleasant to them. Severe colic, "plomb des fosses," is brought on shortly after the inhalation of even very diluted gas—sometimes only a few whiffs. The depression of the nervous system is also distressing.

Besides its action on the nervous system, hydrogen sulphid has a specific action on the blood, changing the oxyhemoglobin to reduced hemoglobin and finally to sulphmethemoglobin,⁵ which is characterized by an absorption spectrum of two bands, one in the red midway between C and D, the other fainter, beginning at D and extending nearly half-way to E.⁶ The blood does not show these in rapid poisoning. Haggard⁷ shows, however, that when an atmosphere containing H₂S is inhaled no

¹ Chemical Pathology, Philadelphia, 1920, p. 590; see also Haggard, Jour. Biol. Chem., 1921, 49, 519.

² Robinson, Jour. Amer. Med. Assoc., 1916, 66, 1611.

³ Burchhardt, Corres. Blatt für Schweitzer Aerzte, 1903, 33, 143.

⁴ Haggard, H. W., Henderson, Y., and Charlton, T. J., Amer. Jour. of Physiol., 1922, 61, 289; Haggard, Jour. Pharm. and Exp. Therap., 1922, 19, 262.

⁵ Kobert, R., Kompendium der toxiologie, Funfte, Auflage, 1912, 208.

⁶ Hoppe-Seyler, Centralbl. f. d. med. Wissensch., p. 433, 1863; also Med. chem. Unters. Berlin, i, p. 151, 1866.

⁷ Jour. Biol. Chem., 1921, 49, 519.

combination of the gas is formed with hemoglobin, nor is there any appreciable amount of sodium sulphid formed in the plasma. Blood plasma in the presence of oxygen possesses the property of rapidly oxidizing hydrogen sulphid. When inhalation has continued for some time the bands have been detected, but must not be confounded with the same bands due to putrefactive processes.¹ Out of 29 cases of poisoning with this gas reported by the chief inspector of factories and workshops for the years of 1908 to 1912, only 5 were fatal.²

Lethal Dose.—The dose is between that of carbon monoxid and prussic acid—0.02 per cent. in the air may have toxic effect; 1 per cent. in the air would be destructive to human life (Letheby). Oliver³ reports death occurring in three minutes in the case of 3 men excavating in a cylinder 48 by 9 feet in the site of an old chemical works. The water in the cylinder contained 12.2 vol. of hydrogen sulphid in 100 vol. of water. Birds are especially sensitive, 1 : 2000 proving fatal, while only 1 : 200 kills dogs. According to Haggard inhalation of hydrogen sulphid kills in a concentration of 7 parts per 10,000 after the lapse of some time.⁴

Postmortem Appearances.—There is nothing characteristic where death has been instantaneous and the autopsy immediate. Later, cases develop such appearances as a brownish, viscid fluid in the nose and throat, and offensive odor from cavities and soft parts of the body. These odors give rise to unpleasant symptoms in those operating, and are more noticeable where the body has remained some time in the poisonous atmosphere. The muscles have a dark color and are irresponsive to electric stimulus; the lungs, liver, and other organs are distended with liquid blood; there is congestion of the right side of the heart, and the body rapidly undergoes putrefaction. When poisoning has occurred from the highly diluted gas the appearances are almost like those due to death from carbon dioxid. There is, however, a tendency to more rapid decomposition and a wide-spread green discoloration of the tissues of the abdomen. Indeed, the usual green discoloration of the abdomen in most cadavers is ascribed to the action of the hydrogen sulphid from intestinal gases on the blood coloring-matter diffused in the tissues.

Tests.—The odor is highly characteristic. Lead acetate paper, sensitive to 1 : 100,000, or in solution 1 : 250,000,⁵ producing a brown or black precipitate or color. Cadmium and arsenic in hydrochloric acid solution produce yellow precipitates of sulphids. These are useful as quantitative tests.

For the determination of hydrogen sulphid in gas⁶ aspirate 0.1 cubic foot of gas through 15 to 25 c.c. of double normal NaOH solution, add

¹ L. Hermann, *Exp. Toxikol.*, 1874, p. 122, Full Discussion of Symptoms and of Blood Spectra, with Citations of Authorities.

² Kober, G. M., and Hanson, W. C., *Diseases of Occupation and Vocational Hygiene*, Philadelphia, P. Blakiston's Son & Co., p. 47.

³ *Lancet*, 1903, 81, 225.

⁴ Haggard, H. W., *The Toxicity of Hydrogen Sulphid*, *Jour. Pharm. and Exp. Therap.*, 1922, 19, 262.

⁵ Wormley, *Micro-Chemistry of Poisons*, 2d ed., Philadelphia, p. 372, 1885.

⁶ Bean, *Amer. Gas Assoc. Monthly*, 1920, 2, 265.

15 to 20 c.c. of normal barium chlorid solution, put in a few drops of phenolphthalein, slightly acidify with 2N, HCl, add 5 c.c. of starch solution, and titrate with N/10 standard iodine solution until a permanent blue color is obtained. The number of cubic centimeters of iodine solution used multiplied by the factor (26.3) gives grains of H_2S per 100 cubic feet of gas.¹

Solutions of hydrogen sulphid become blue when treated with $\frac{1}{50}$ of their volume of a solution of fuming hydrochloric acid, a few milligrams of para-amidomethylaniline sulphate, and 1 or 2 drops of a dilute solution of ferric chlorid (Caro-Fischer test). The reaction is very sharp, 0.00009 to 0.0000182 gram of H_2S per liter being recognizable.² Boneko recommends this test in the analysis of urine.

A conclusive toxicologic analysis can be made only immediately after death and best at the place where the accident occurred. A bright silver or copper coin inserted in the muscles or mouth becomes tarnished. Lead-paper is blackened. Blood spectra are rarely obtainable.

SEWER AIR

The poisonous effects of the air of sewers, cesspools, and privy vaults are due to hydrogen sulphid, ammonium sulphid, other undetermined gases, and to carbon dioxide and nitrogen. In many instances the asphyxiation is due solely to want of oxygen. The greatest danger is due to the presence of the sulphids. Paris sewer air gave on analysis in 100 parts—oxygen, 13.79; nitrogen, 81.21; carbon dioxide, 2.01; hydrogen sulphid, 2.99.³

According to French ordinances, 5 kilos of ferrous sulphate are to be added to each cubic meter of night-soil. The mass must be well stirred to expel gas. Many accidents result from not taking this precaution. In entering such an atmosphere a wet sponge should be worn or one of the types of respirator mentioned under carbon monoxide poisoning. In many works men must be so provided.⁴

SULPHUR DIOXID

(Chemical formula, $SO_2 = 64$. Synonym, *Sulphurous Acid*)

Found in nature in the vicinity of volcanoes. It is the product of burning sulphur or of metallic sulphids with air or oxygen. It frequently contaminates the air near metallurgic works, destroying vegetation. It is present in noticeable amount in the air of towns where

¹ Czak, Jour. f. Gasbel., 1919, 62, 483; see Bunte, Ibid., 1888, 31, 898; Behrend and Kast, Ibid., 1889, 32, 158.

² Dragendorff, Ermittlung von Giften, 4th ed., Göttingen, 1895, p. 64.

³ Taylor, Medical Jurisprudence, 12th Amer. ed., 1897, p. 486.

⁴ J. Pohl, Arch. exp. Pharm., 1887, xxii, 1. K. B. Lehman, Arch. f. Hygiene, 1892, xiv, 135. Koppel, Litterar. Zusammenst. der von 1880–1890 in der Weltliter., beschrieb. Fälle Vergiftungen von Menschen durch Blutgifte, Inaug. Diss. Dorpat., 1891, p. 118. J. Deichstetter, Friedreich's Blätter der ger. Med. und Sanitäts-Polizei, 1896, lxxiv, 103. Th. Weyl, Gewerbe Hygiene, Jena, 1896. Parke, Hygiene, Amer. edition, 1884, p. 146. Woodman and Tidy, Forensic Medicine and Toxicology, Philadelphia, 1877, p. 494. Clark. H. W., Sewer Following Boston Explosion, Eng. Record, 1914, 70, 606.

coal containing sulphur is burnt. It is given off in the spontaneous combustion of coal. It is very noticeable in tunnels and underground railways, where the ventilation is poor.

In 1897 the whole population of Mount Vernon, N. Y., suffered from the suffocating fumes of the gas. The source was the improper purification of the illuminating gas. The air of homes and the streets was filled with sulphur dioxide.

It is produced in the refining of petroleum in large quantities. It is decomposed by sunlight into sulphur trioxid and free sulphur, thus producing part of the haze over large cities. It is readily oxidized to sulphur trioxid, which in its turn yields sulphuric acid when united to water. This acid causes destruction to property. Owing to the solubility of each of these oxids, the atmosphere is never found to have a considerable quantity of either. It is prepared either by the combustion of sulphur or by the deoxidation of sulphuric acid by charcoal or metals.

Workmen in many trades are constantly exposed to its action. Its intense odor fortunately prevents accidents.

It is an irrespirable, colorless gas, possessing the odor of burning brimstone. It is heavier than the air (specific gravity, 2.25). It is condensible to a clear liquid at -18° C., and is solid at -76° C. The liquid has a specific gravity of 1.45 at -20° C. and boils at -8° C. The liquid is sold in glass siphons or in metallic holders, and is much used in disinfection and artificial refrigeration.

The gas is very soluble, water absorbing 43.5 times its volume, and forming sulphurous acid, H_2SO_3 . The concentration of free sulphur dioxide and sulphurous acid in water and in calcium and magnesium hydrogen sulphid solutions is exactly and directly proportional to the partial pressure of sulphur dioxide in the gases above the solution at all temperatures, alkali concentrations, and pressures.¹

Sulphur candles and liquid SO_2 are much used in domestic disinfection. The gas extinguishes flame even in the presence of much air. It is a powerful reducing agent. It is a preservative and a bleaching agent.

Symptoms.—The first are those of suffocation. The glottis closes against it. The air-passages are highly irritated through the formation of sulphurous acid on their surface. Coughing and sneezing are speedily induced. The remoter action is on the blood, reducing the same and decomposing it. Both men and animals may be habituated to its inhalation. Air containing from 0.03 to 0.04 gram per thousand did not affect workmen more severely than did from 0.01 to 0.02 those unaccustomed to breathing the gas.² Mice were affected more severely when 0.5 grain of sulphur was burnt in a receiver than when, after repeated exposures to such air, 10 grains were burnt in the same vessel.³ Letheby found the trainmen of the London Underground Railroad

¹ The Jour. of the Amer. Chem. Society, 1922, 44, No. 9, 1925.

² B. K. Lehmann, Arch. f. Hygiene, 1893, xviii, 180.

³ Tidy, Forensic Medicine and Toxicology, 1877, p. 495.

little affected by the constant breathing of the tainted atmosphere. Experiments on rabbits, mice, and guinea-pigs showed 0.04 vol. per cent. sufficient to bring on marked symptoms of poisoning, while 0.3 per cent. proved fatal.¹ Others claim that from 1 to 3 per cent. can be respired without ill effects (Hist).² The gas produced the same effect whether breathed through the nose or by tube introduced in the trachea. The cornea becomes opaque, and there are dyspnea, cyanosis, and convulsions. Taken internally, there are catarrh of the stomach and chronic sulphuric acid poisoning. According to Kobert³ sulphur dioxid has been used for murder only once, and sulphurous acid only once with suicidal intent.

The effects on vegetation are greater than on animals. Suits for damages against works for the destruction of trees and other plants are frequent.⁴

Treatment.—Proper prophylactic measures; masks for workmen containing a wet sponge, or, better, an army gas mask. Fieldner and Katz⁵ believe that the Tissart mask in combination with a 100 cubic inch soda lime canister will prove the best for exclusive use in SO₂ and acid gases in concentrations less than 2 per cent.; ventilation; restriction of quantity used to preserve food or drink. Mild alkalis serve as antidotes.

Postmortem Appearances.—Those of asphyxia. The blood is very dark and has in part an acid reaction. The hemoglobin is changed first through loss of oxygen, then by decomposition, to hematin, as with mineral acids. The respiratory tract is catarrhal or even croupous in aspect, due to the action of the acid. The lungs are partly edematous.

Tests.—Intense suffocating odor. Blue color with starch and iodic acid; sensitive to 1 : 3000. In foods and drinks it is tested for after being reduced to hydrogen sulphid by zinc and hydrochloric acid⁶; or acidify 100 grams of material with tartaric or phosphoric acid and collect the distillate in an acidified solution of potassium iodid to which starch has been added. The steam from the distilling flask before entering the condenser should be passed through a flask containing 40 c.c. of a 2 per cent. neutral solution of cadmium chlorid to remove hydrogen sulphid. The free iodine in the distillate can be titrated or the sulphur dioxid can be oxidized and precipitated with barium chlorid, after acidifying with hydrochloric acid.⁷

¹ Ogata, Arch. f. Hygiene, 1884, xi, 246.

² Th. Weyl, Hygiene der chem. Gross-Industrie, Jena, 1896.

³ Kobert, R., Kompendium der toxiologie Fünfte Auflage, 1912, 147.

⁴ Schroeder and Reuss, Die Beschädigung der Vegetation durch Rauch und die Huettenrauch-Schaden, 1883; also Just and Blaine, Landw. Versuchsst., pt. ii, 1889. Withrow, J. R., Atmospheric Pollution from Sulfuric and Plant Fumes, Chem. and Met. Eng., 1922, 26, 972. Perrott, G., St. L., Sulfur Dioxid as a Factor in the Smoke Problem of Salt Lake City, Bureau of Mines, Report of Investigations, 1920, No. 2128.

⁵ Eng. Mining Jour. 1919, 107, 693.

⁶ L. Hermann, Exp. Toxiologie, Berlin, 1874, p. 157.

⁷ Leach, Food Inspection and Analysis, 4 ed., 1920, p. 238, 896; Spiess, H., Chem. Ztg., 1922, 46, 405.

NITROGEN MONOXID

(Chemical formula, $N_2O = 44$. Synonyms, *Nitrous Oxid*; *Laughing Gas*)

Laughing-gas is colorless, with a sweetish taste and smell. Water dissolves its own bulk. It supports combustion, but not life, as Davy supposed. It is eliminated from the blood unchanged. It has a specific gravity of 1.53. It becomes liquid at $+7^\circ C.$ and 40 atmospheres pressure; solidifies at $-102^\circ C.$ at common pressure. It is sold in a liquid state in wrought-iron containers, and is used from these as an anesthetic. It is prepared for this purpose by heating ammonium nitrate, and must be carefully purified. The gas is usually purified by passing through a wash bottle with water to take up dust, then through ferrous sulphate to remove nitric oxid and ammonia, through sodium hydrate solution to remove chlorin and its oxids, and sulphuric anhydrid to remove nitrogen oxids, carbon dioxid, sulphur dioxid, and hydrogen sulphid.¹ Lehman found that 0.0008 to 0.0017 per cent. by vol. of nitric oxid can be tolerated for hours, while 0.0106 to 0.0177 per cent. by vol. is more dangerous. Hamilton records 1389 cases of poisoning by nitrogen oxid in which there were 28 deaths. A specimen of blood from 1 of these cases was examined by McNally and found to be slightly acid and contained traces of nitric oxid.²

Symptoms.—When breathed in small quantity it produces a delicious tingling sensation and tends to induce laughter, hence its names, “paradise gas” and “laughing gas.” Persons differ greatly in what they do when under the influence of the gas at this stage. Its anesthetic effect on a young man, Cooley, who bruised his shins while dancing under its influence, yet felt no pain, was noticed by Dr. Horace Wells, of Hartford, and led to its use in dentistry. Gardiner Q. Colton administered the gas to Wells at the latter’s request, and Dr. Riggs extracted the first tooth without pain December 11, 1844. The gas fell into disuse, however, until 1863, when its use was revived by Colton. From February 4, 1864 the patients have inscribed their names on a scroll. Doremus witnessed January 17, 1898 gas administered to the 196,470th patient. No accidents had happened. By covering the nose and mouth with a respirator and keeping the patient’s head slightly forward, the breathing is easy, unconsciousness speedy, the tint of the skin inclined to be blue, but not livid, insensibility complete, and recovery rapid. The use of the gas for prolonged surgical operations is growing, since there is rarely any subsequent vomiting. Access of air or 20 per cent. oxygen, or this mixture breathed under pressure, is employed, since nitrous oxid cannot replace oxygen for respiration.³ The brain is first paralyzed, then the center of sensation of pain, then consciousness. The action then extends to the spinal cord, medulla oblongata, and finally to the heart. Asphyxia follows prolonged inhalation with-

¹ Hart and Marshall, *British Dental Jour.*, 1914, 35, 77, June 15.

² Hamilton, A., *Industrial Poisons Encountered in the Manufacture of Explosives*, *Jour. Amer. Med. Assoc.*, 1917, 68, 1447. See Welsh, G. A., *Effect of the Inhalation of Gases*, *Jour. Ind. Hyg.*, 1921, 2, 328; Jacoulet, F., *Acute Poisoning from Nitrous Fumes*, *Paris Med.*, 1920, 10, 369.

³ L. Hermann, *Exp. Toxikologie*, Berlin, 1874, p. 243.

out oxygen. The blood-pressure is augmented, and it is dangerous, therefore, to use it on patients with a weakened vascular system. Arterial blood shaken with the gas becomes dark, and venous blood, though shaken, does not become arterial. It does not combine with the blood, though this is claimed. The erythrocytes decrease 25 per cent. on the average under nitrous oxid and oxygen anesthetization¹ for one-half hour. The H ion concentration is increased in the blood, spinal fluid, and bile, with a progressive decrease in the alkaline reserve of the blood. Crile² had over 1500 cases without a death. The death-rate is about 1 in 100,000. Considering the short interval of time that nitrous oxid is inhaled and the large dilution of air and oxygen, the amounts of gaseous impurities found are too small to have any effect on a person. Death during the administration has not been due to poisonous action of the gas, but to asphyxia or other cause.³

Treatment.—Fresh air, oxygen, and stimulants.

Postmortem Appearances.—No changes observable in man or animals even after many hours' narcosis except that the blood is of dark color.

Tests.—Solubility of the gas in alcohol. Explosion with hydrogen leaves a residue of nitrogen and water.

NITRIC OXID (NO = 30)

Also NITROUS ANHYDRID ($N_2O_3 = 76$); NITRIC PEROXID ($NO_2 = 46$)

Nitric oxid is a highly poisonous, irrespirable gas. It is colorless, nearly insoluble in water, but turns red in air giving N_2O_3 , and NO_2 , both of which dissolve. It is obtained by the deoxidation of nitric acid in voltaic batteries, or by the action of this acid on charcoal, metals, cotton, and vegetable fiber and by animal tissues. It is frequently evolved in great quantities in manufactories and laboratories, and must be especially guarded against by proper ventilation or by masks. Unfortunately, there is as yet no good absorbing respirator for these gases. Works, therefore, need constant supervision to protect employees.

Symptoms.—Habitually breathed in small quantities and great dilution it produces severe chronic diseases. In acute poisoning immediate dyspnea, tightness of chest, coughing, fainting, cyanosis, diarrhea, and collapse. Death within forty hours, though symptoms of slight poisoning are delayed, in which case the first symptoms are headache, desire for fresh air, thirst, and then suddenly symptoms of aggravated character—distress of breathing, anxiety depicted on face, cold perspiration, protruding eyeballs, and spasmodic coughing, followed by vomiting.

Blood drawn on venesection is tarry, thick, black, and coagulates rapidly. It is of diminished alkalinity, and on dilution becomes red and

¹ Casto, Dental Cosmos, 1917, 59, 415; Amer. Jour. of Surg. Anes. Supplement, 1917, 32, 44.

² Jour. Amer. Med. Assoc., 1916, 67, 1830.

³ Kobert, Lehrbuch der Intoxikationen, Stuttgart, 1893, p. 550; Tidy, Forensic Medicine and Toxicology, Philadelphia, 1887, p. 490; Luke, New York Med. Jour., 1915, 101, p. 207; Bruxton, British Med. Jour., 1916, 2, 159.

shows the oxyhemoglobin spectrum. Although Hermann¹ was able to obtain a definite compound of nitric oxid and hemoglobin, *ex corpus*, Belky² denies the possibility of its formation in poisoning by nitric oxid.

Treatment.—Removal of the person from the vitiated atmosphere; in commencing edema of the lungs administer atropin. When edema is absent, inhalations of vapor of water and a little ammonia. In cyanosis, alkaline salt injections.

Postmortem Appearances.—Congestion of the larynx and trachea and edema of the lungs. Brown colored serum from any incision of the lungs. Veins of the pia mater full. The blood reacts acid.

Tests.—Starch and potassium iodid, after cautious acidulation with sulphuric acid, give blue color and detect traces. The color and odor of the gaseous mixture breathed are characteristic.³

MUSTARD GAS⁴

(Synonym, *Yperite*)

The use of the toxic shell has been divided into three periods by Goss.⁵ During the first period, May, 1915 to July, 1916, only lacrimatory shells were used; while these lacrimators had considerable harassing power, no deaths were reported. Lethal shells came into use July, 1916. In addition to the lacrimators, shells were employed containing phosgene, diphosgene, and chlorpicrin. The third period began with the appearance of mustard gas at Ypres, July 12, 1917.

Thiodiglycolchlorid, B. B. dichlorethylsulphid, $(\text{CH}_2\text{ClCH}_2)_2\text{S}$, commonly known after July, 1917 as "mustard gas," was first made by Victor Meyer in 1882. It is a heavy oily fluid, specific gravity 1.274 at 20° C.⁶; sinking below water and not miscible with it; light straw color, pink or brown; of neutral reaction; having a sweetish ethereal odor, but slightly suggestive of sulphur compounds; soluble in alcohol and other organic solvents. It boils at 217° C. with decomposition; crystallizes in long prisms at 0° C.⁷ Adams and Williamson⁸ found that the freezing-point ranges from 13.9° C. at one megabar to 38.9° C. at 1800 megabars. The latent heat of melting is 25 calories per gram, and the freezing-point lowering constant is 6.5° C. (1 mol. solute per 1000 g. of solvent). The peculiar property of the gas to volatilize and recondense with variations of temperature explains its persistence about the bombarded areas.

Symptoms.—While exposed to the gas there is but slight lacrimation,⁹ nasal, or salivary secretions, no coughing, bronchial or laryngeal

¹ L. Hermann, *Exp. Toxikologie*, Berlin, 1874, p. 112.

² Belky, *Virchow's Arch.*, 1886, clx, 160; *Lehre der schädlichen Gase*, 1865.

³ Moir, James, *The Determination of Nitrous Fumes in the Air with Special Reference to Fuse Igniters*, J. S. African Assoc. Anal. Chem., 1921, 4, 3.

⁴ See Chapter on Death from Asphyxia, p. 398.

⁵ Jour. Indust. and Engin. Chem., 1919, ii, 829.

⁶ Smith, *Jour. Pharmacol. and Exper. Therap.*, 1919, 13, 1; W. J. Pope, *Jour. Soc. Chem. Ind.*, 1919, 38, 344.

⁷ *Berichte*, vol. 19, p. 3260.

⁸ *Jour. Wash. Acad. Sci.*, 1919, 9, 30.

⁹ Winternitz, *Mil. Surgeon*, 1919, 44, 476.

spasm, no tremors or convulsions. After the first few hours of exposure there is a feeling of depression with an anorexia, some vomiting and diarrhea. The eyes become red and very uncomfortable. Prolonged exposure to small concentrations cause laryngitis and loss of voice sufficient to put the men out of action. After eight to twelve hours the pulse is slow and irregular, respirations irregular and labored, frequent coughing, profuse salivary and nasal discharge. In severe cases bronchitis and pneumonia may develop after thirty-six hours.¹

This gas in extreme dilutions is an irritant for animal tissue when in direct contact. The degree of injury is proportionate to the amount of gas, time of exposure, the individual susceptibility, moisture, warmth, pressure, and friction. In the manufacture of mustard gas the men frequently complained of the irritant action of the gas in the axillary and pubic regions when the skin became moist with perspiration. Clowes² claims from experimental work that the moistened surface gave burns two or three times as severe as those on dry surfaces. The penetration of the gas through a heavy duct and an impregnated fabric was facilitated by the addition of 4 or 5 per cent. of water and partially inhibited by the addition of larger amounts of water. The first effect upon the skin is a hyperemia followed by vesication, eschar formation, sloughing and slow healing, with more or less pigmentation³; in some instances the skin peeled in flakes or the redness changed to pigmentation.⁴ Secondary infections and gangrene of the eschars occur invariably when not properly treated. Krumbhaar⁵ claims mustard gas exerts a direct toxic action on the bone-marrow, which by depleting the leukocytes of the circulation has an important bearing on the inability to resist secondary infection. Moorhead⁶ asserts from the investigation of 35 cases that the rate of coagulability is increased, that the red blood-cells are increased per cubic millimeter, and that the hemoglobin is high, due probably to stagnation of blood in the peripheral capillaries.

An injury to the conjunctiva of the eyes is shown by the development of catarrhal, seropurulent, or a purulent conjunctivitis. Pupil reflexes normal, marked swelling of the eyelids. Irritation and photophobia are so severe in some cases that a few drops of cocain and a lid elevator must be used to make an examination.⁷ Less severe cases healed in three or four days. The cornea (Scott and Miller) may be killed throughout the entire thickness at the vertex, while in the mildest cases a slight cloudiness is noted. The gas acting upon the respiratory tract causes aphonia, which may come on suddenly or be preceded by a cough lasting for two or three days. Tracheitis and bronchitis then

¹ Warthin and Weller, *Jour. Lab. and Clin. Med.*, 1917-18, iii, 447; 1918-19, iv, 229; Mandel and Gibson, *Jour. Amer. Med. Assoc.*, 1917, xlix, 1970.

² *Jour. Indust. and Eng. Chem.*, 1919, 11, 1017.

³ Scott and Miller, *Proc. Soc. Exper. Biol. and Med.*, 1918-19, xvi, 143.

⁴ Stack, Combs, Rolfe, *Bristol Med.-Chir. Jour.*, 1919-20, xxxvii, 151.

⁵ *Jour. Med. Research*, 1919, 40, 497.

⁶ *Dublin Jour. Med. Sci.*, 1919, cxlvii, 1. See Zunz, E., *Changes in the Blood in the Cause of Intoxication by Yperite*, *Ambulance de l'Océan*, 1919, 2, 411.

⁷ Derby, *Amer. Jour. Med. Sci.*, 1918, 156, 733.

develop. At the end of three days the patient discharges an abundant mucous sputum; breathing is difficult except in an erect position. Respiratory affections are most intractible and frequently relapse without apparent reason.¹

Pathology.—The respiratory lesions are proportionate to the concentration and length of exposure. In the mildest cases a superficial degeneration and necrosis of the epithelium of the mucous membrane obtains, with congestion and edema. In more severe lesions a deeper necrosis of the mucosa of the respiratory tract is noted, with the formation of a diphtheric membrane in the anterior nares, pharynx, larynx, and upper portions of the trachea (Warthin and Weller²). An examination of the internal organs offers nothing of a specific nature. The lungs show extreme passive congestion, the cut surface is dark crimson, rather dry as a rule, apparently pneumonic.³ The tissue feels doughy, with a loss of elasticity. The air sacs remain distended until pressed (Winternitz). Sections show that the condition is a mixed pneumonia, hemorrhagic in every instance, and in some necrotic. In milder cases there is an intense engorgement of the capillaries, with desquamation of the vesicular endothelium with catarrhal exudate. Bronchioles show desquamated epithelium and leukocytes. Later, when the pneumonic process spreads, vessels become choked with leukocytes and red blood-cells. Large patches or whole lobes become hepatized and lung tissue undergoes necrosis. The kidneys show some cloudy swelling. The stomach frequently shows a hemorrhagic gastritis. Direct application of mustard gas to the mucosa of the stomach or intestine by means of contaminated food, produces localized degeneration, necrosis, and ulceration, similar to lesions of the respiratory tract (Warthin and Weller). In the severe cases, large erythematous patches appear upon the skin in twelve hours after exposure with large bullæ containing serous or seropurulent fluid. Occasionally, particularly on the scrotum, the large blisters are replaced by small purulent vesicles surrounding the roots of the hairs.

Treatment.—Principally, remove the remaining gas, lessen necrosis, prevent infection, and promote healing. Washing the eyes with a solution of bicarbonate of soda, 30 parts per 1000, was found to be prophylactic against the conjunctivitis. For the burns, use a bicarbonate solution and a dressing of Vincent's powder (boric acid and calcium hypochlorit) or use air-excluding dressings as paraffin sprays, olive oil, and vaselin. Williams⁴ recommends an ointment containing zinc oxid 45 per cent., linseed oil 30 per cent., lard 10 per cent., neutral wool fat 15 per cent. Ointment is for preventive purposes and has little healing

¹ Giraud, *Jour. de med. et de chir. prat.*, 1917, lxxxviii, 890-895.

² See Flury, *Ztschr. f. exp. med.*, 1921, 13, 367; Heitzman, *Ibid.*, 484.

³ Boxwell, Dublin, *Jour. Med. Sci.*, 1919, cxlvii, 7.

⁴ *Jour. Amer. Pharm. Assoc.*, 1919, 8, 824; see also Hanzlik and Tarr, *The Comparative Skin Irritant Properties of Mustard Gas and Other Agents*, *Jour. Pharmacol. and Exper. Therap.*, 1919-1920, 14, 221; Sollmann, *Mustard Gas, Influence of Solvents and Antidotes in Skin Lesions*, *Jour. Pharmacol. and Exper. Therap.*, 1918-1919, 12, 311; McDonagh, *Treatment of Mustard Gas Poisoning*, *Med. Press and Circular*, London, 1918, 106, 365.

value. Ointment was rubbed in twice daily to crotch, armpits, hands and feet, and exposed portions of face. The fluid intake should be forced when the urine is concentrated. Pressure should be removed from all parts. Change of clothing and dry bathing should be practiced, as the gas acts better in the presence of water.

Sequelæ.—There is an apparent increased susceptibility of the patient to influenza, bronchitis, pneumonia, tuberculosis, chronic eczema, itching and desquamative dermatitis and pigmentation.

Tests.—A quantitative determination of traces of mustard gas in the air has been described by Yablick, Perrott and Furman¹ based upon the reduction of 1 per cent. solution of selenious acid in 1 : 1 sulphuric acid by dichlorethylsulphid to an orange-red suspension of selenium, the solution being heated to 85° C. to hasten the reaction. In this way they were able to detect as low as 0.005 mgs. of the dichlorethylsulphid.²

ARSENIURETTED HYDROGEN³

Poisoning by arseniuretted hydrogen⁴ at the present time is relatively rare, although it is a well-known gas found in chemical laboratories. It is known under various names, as arsin, arsonia, arsenamin, and arseniuretted hydrogen. Arsin (AsH_3), molecular weight 77.98, specific gravity 2.695, weight of a liter 3.4944 grams, contains 96.12 per cent. arsenic and 3.88 per cent. hydrogen. It is a colorless, inflammable gas, having a strong garlic odor; soluble in five volumes of water free from air; neutral in reaction. Arsin can be liquefied at -120°C. , solidifying at -118.9°C. The products of combustion are arsenious acid and water.



If the gas be passed through a tube a portion of which is heated to redness, the gas will be decomposed and the metal deposited in a cooler portion of the tube. (See Marsh Test in Section on Arsenic.) The gas burns with a blue-white flame, which is only seen when the gas is allowed to stream through a platinum jet and ignited, otherwise, as in the usual Marsh test, the flame is colored from the glass. A cold surface held above the flame becomes coated with a white crystalline deposit of the trioxid. If the flame be cooled by the introduction of a cold surface into it, the arsenic is deposited upon the cold surface.

Air and arsin form an explosive mixture. Chlorin decomposes the gas setting free arsenic as a brown cloud, any excess of chlorin combining

¹ Jour. Amer. Chem. Soc., 1920, 42, ii, 266.

² Smith, Mechanism of Absorption of Mustard Gas, Jour. Pharmacol. and Exper. Therap., 1919, 13, 1; Henry, Gas Offense in the U. S., Jour. Indust. and Eng. Chem., 1919, 11, 5; Heritage, Mech. Eng., 1919, 41, 806; Hill, G., Jour. Roy. Army Med. Corps, 1920, 334, Pathology of War Poison Gases; Coney and Barron, Pathology of Mustard Gas Poisoning, Amer. Jour. Med. Sci., 1919, 157, 808; Hermann, G. R., Clinical Pathology of Mustard Gas Poisoning, Jour. Lab. and Clinical Med., 1918, iv, 1; Flury, F., et al, War Gas Poisoning, Ztschr. f. Exp. Med., 1921, 13, 1-578.

³ See Chapters on Inorganic Poisons, p. 242; Death from Asphyxia, p. 415; and Industrial Toxicology, p. 783.

⁴ See Section on Arsenic, p. 208.

with arsenic as a chlorid. Arseniuretted hydrogen and sulphuretted hydrogen may be evolved at ordinary temperatures without decomposition, but at a temperature of 350° C. are decomposed, sulphid of arsenic and hydrogen being formed. Many metals have the property of decomposing the gas at high temperatures, setting hydrogen free.

Arsin is found in the arts in the bronzing of brass, in the desilvering of lead by zinc, in the tinning of sheet iron, from the use of acids containing arsenic as impurity, from storage batteries, or from the application of arsenic itself. Glaister,¹ Maljean,² and Crone³ report cases of poisoning from gases used in inflating war balloons. Proles⁴ reports 39 cases of poisoning by arsin, 19 of which proved fatal within three to twenty-four days. Twelve were chemists, 11 were engaged in filling toy balloons, 7 were anilin workers, 5 were lead smelters, 3 were balloonists, 1 the occupation was not stated. Ramhousek⁵ reports 5 cases which occurred in Breslau in 1902, of whom 3 died from inhaling this in the filling of toy balloons. Koelsch⁶ reports 11 cases which occurred during the manufacture of V. iron, from ore containing 0.3 per cent. arsenic, which was extracted with H_2SO_4 . The work had been going on for three years without a mishap, when 11 out of 13 men were poisoned, 1 dying.⁷ Glaister reports 120 cases of poisoning classified as follows:

1. Chemical operations	23
2. Trade processes	73
3. Military ballooning	16
4. Domestic environment ⁷	6
5. Causes not known	2
	120

Legge,⁸ reports 2 cases of arsin poisoning from the cleaning out of Welden mud from a Welden chlorin still, in which hydrochloric acid was used containing 0.292 per cent. of arsenious acid. Ferrosilicon, in the presence of moist air, gives off arseniuretted hydrogen and phosphuretted hydrogen; 11 deaths in steerage passengers were reported from this source. The AsH_3 is liberated from Ca_3As_2 which is present in the ferrosilicon as an impurity.⁹ The steerage passengers were lodged over the hold containing a consignment of ferrosilicon. Glaister cites another instance in which 4 patients died on a Swedish steamer from the same source of the gas. Dudley¹⁰ and Giordona¹¹ report

¹ Actes du 11 Congress Internat. des Maladies Professioneles Bruxelles, 1912.

² Archives de Med. et de Pharm. Milit., vol. xxxv, p. 82.

³ Deutsche Militararztl Zeitschrift, 1900, xxix, 139.

⁴ Bl. f. Gerichtl. Med., 1901, p. 171.

⁵ Industrial Poisoning, London, 1913.

⁶ Zent. für Gewerbehygiene, 1920, 8, 121.

⁷ A volatile arsenic compound is produced, which has been supposed to be arsin, but more recent investigations have shown this volatile substance to be diethylarsin; Abba, Bakt. Centr., 264 Abt., 1898, lv, 806; Sanger, Proc. Amer. Acad. Arts and Sc., 1894, xxix, 112; Maasen, Arb. d. kais. Gesundheitsamte, 1902, xviii, 475.

⁸ Kober and Hanson, Diseases of Occupational and Vocational Hygiene, p. 9.

⁹ Hamilton, Chem. Trade Jour., 1919, 65, 365.

¹⁰ Jour. Indust. Hygiene, 1919, p. 215.

¹¹ U. S. Naval Medical Bulletin, 1917, 11, 342.

severe cases of poisoning from arsin generated in the batteries of submarines. In Dudley's case, the lead plates contained 0.2 per cent. arsenic; in Giordona's case, the asbestos bags surrounding the plates to prevent lead oxid crystals from dropping to the bottom, contained arsenic. All of the reported cases have been accidental, caused by the inhalation of hydrogen generated from materials containing arsenic as an impurity, the arsin being evolved simultaneously. One of the earliest cases recorded was that of the chemist Gehlen, who met his death while experimenting upon the action of hot concentrated caustic potash upon arsenic trioxid.

Arseniuretted hydrogen is one of the most active of the mineral compounds of arsenic, containing 96 per cent. of arsenic, and part of its violent action can be attributed to the more rapid absorption by the pulmonary surface than that of dissolved arsenicals by the alimentary tract. Much more than 0.01 mg. arsenic can be taken in, as arsin, without fatal results.¹ In Dudley's cases the hemoglobin varied between 48 and 78 per cent. on admission. The red blood-cells in 2 men were under 2,000,000 per cubic centimeter, 12 had 2,000,000 to 3,000,000, 10 cases had 3,000,000 to 4,000,000, and 6 cases had over 4,000,000. The number of white cells stayed about normal. Joly and Nabias² found that in dogs poisoned by arsin the solution of hemoglobin is so extensive that one-half of the total amount is in the serum, from which it passes to the serous fluids and urine, being converted into methemoglobin. Herbert and Heim, in experiments upon animals, found that 3.5 c.c. per liter is rapidly fatal to mammals, and 0.09 c.c. per liter to birds; and that in concentrations below 0.05 c.c. per liter for mammals and 0.02 c.c. per liter with birds it is without distinctly detrimental results.³ Fühner⁴ found paramaecium and other protozoa more resistant to arsin than to arsenious acid of the same strength.

Symptoms.—In mild cases of poisoning by arsin the respiration shows a slight rise above the normal; there is dryness and burning in the throat; temperature is normal; pulse may be high, but gradually settles down to normal. Continued exposure to the gas causes vomiting, accompanied in some cases by a griping and burning sensation in the upper abdomen. In most of the cases the attack began with a feeling of faintness and giddiness, chills, more or less severe, and pain in the kidneys. In the submarine cases the color of the urine changed to a brown, then to a red color. The color became normal in four days and the albumin which was present disappeared. Jaundice was an absolutely constant sign in the mild and severe forms of poisoning. In some of the cases the conjunctivæ and skin become yellow on the second day, the color of the skin deepening to a bronze or copper, which gradually diminishes toward the fifth or sixth day. In a few cases⁵ the jaundice was the first symptom to appear, the workmen noticing

¹ Wignall, *Brit. Med. Jour.*, 1920, 1, 826.

² *C. r. Ac. Sc.*, 1890, ex, 666.

³ Herbert and Heim, *Bull. Soc. Chim. de France*, 1907, 4s., ii, 571, 573.

⁴ *Arch. Exp. Path. Pharm.*, 1918, 82, 44.

⁵ Trost, *Vierteljahrsschrift f. gericht Med.*, 1873, xviii, 6.

the yellow color while at work; and in Valette's 2 cases the sclera was observed to be yellow one hour after exposure.¹

In all of the reports of poisoning by arseniuretted hydrogen the prominent symptoms were the lumbar pain, the icterus, and hemoglobinuria. In addition to hemolysis, AsH_3 acts on the central (narcosis and paralysis), but not on the peripheral nervous system.² The lumbar pains occur early and are severe in most cases. The urine passed is bright red, dark brown, or black in color, coagulates almost solid by heat. The quantity of urine passed is usually normal or somewhat increased at first, followed by a marked diminution or complete suppression.

In Giordana's cases recovery occurred in fifteen days. The shortest period of complete recovery was in Valette's case in eight days. The shortest time in which death occurred was in twenty-three hours in 1 of Chevalier and Chaignot's cases.³ The average duration of 25 cases was four days and four and one-half hours. The longest survival in a fatal case was twenty-eight days reported by Valette.⁴

Postmortem appearances after death from arseniuretted hydrogen are characterized by the dirty yellow or bronzed discoloration of the skin. All of the tissues are more or less yellow. The liver is normal in size or somewhat enlarged, may be of a deep indigo color, yellow, or gray. The gall-bladder always contains much bile and is sometimes distended. The kidneys are brown, chocolate brown to a black, enlarged, and highly congested. The mucous membrane of the stomach is slate or yellow in color. In 1 of the cases reported by Legge, $\frac{1}{350}$ grain of arsenic was found in 11 ounces of viscera. In Trost's case arsenic was found in all parts of the body. In nearly all of the cases where an analysis was made of the organs, the arsenic was found in undetermined traces, an exception being that of Lesser's case,⁵ in which Bischoff found the following amounts of arsenic in milligrams of arsenic trioxid in 100 grams of tissue; in the liver, 1.308; kidneys, 0.127; spleen, 0.617; blood from the heart, 0.54; stomach, 0; heart, traces; intestines and contents, 0.065; brain, 0.05. Death occurred eleven days after the inhalation.

Tests.—The presence of traces of arseniuretted hydrogen in air may be detected by passing a large volume first through a solution of cuprous chlorid to remove hydrogen sulphid, phosphin and stibin, and then over paper moistened with mercuric chlorid, which is colored yellow, 0.02 c.c. per liter giving a distinct reaction. By using standard bands for comparison, as in the Gutzeit method for arsenic, extremely small amounts of arsin may be detected. Sparth⁶ claims AsH_3 could not be isolated from organs by distilling *in vacuo*.

¹ Ambrose Tardieu, *Etude Medico-legale sur l'Empoisonnement*, 1875, p. 449.

² V. Oettinger, *Arch. Exp. Path. Pharm.*, 1917, 80, 288.

³ *Intox.*, p. le gas d. ballons, 1904.

⁴ *Lyon Med.*, 1870, iv, 440.

⁵ *Vrtljschr. f. ger Med.*, 1897, 3 f., xiv, 296.

⁶ *Chem. Zent.*, 1918, 11, 134.

DEATH FROM ASPHYXIA

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Definition.—By the term *asphyxia* is meant the fatal or deleterious result of any interference with the normal processes of respiration. Respiration in each of its divisions of inspiration and expiration is a threefold act. Inspiration, for example, includes the entrance of atmospheric air along the respiratory passages to the pulmonary alveoli, the diffusion of its oxygen through the animal structures separating it from the blood and combination with the latter, the convection of the oxygen to the cellular elements of the body and its transference to these. Expiration is the expression of the reverse phenomena resulting in the elimination of carbon dioxid. Each of these is physiologically divisible into an external and an internal process, the passage of the gases in question through the walls of the pulmonary vessels and air-spaces marking the separation between these divisions. The process of asphyxiation may therefore be technically understood to include any interferences with the passage of properly oxygenated air along the respiratory tracts, the prevention of the lungs to receive such air entering by these passages, and any interference with the proper power of the blood to combine with and convey oxygen or carbon dioxid to or from the tissues. Further, although of little concern in the scope of the present discussion, alterations of the nervous apparatus presiding over the function of respiration should not be neglected from a purely technical point of view.

It is clear, however, that our ordinary ideas of asphyxiation do not embrace all these possibilities. For example, the convection of oxygen by the blood may have been prevented by circulatory failure; and while the term asphyxia (*a*, absence of; *σφύξις*, pulse) was originally intended to indicate this very condition, such meaning is not longer held either popularly or generally by the medical profession. So also, the various interferences with the intricate processes of cellular respiration, or of the relatively unimportant skin respiration, are not to be regarded as essential portions of the meaning of the term in its ordinary sense. On the other hand, the results of the inhalation of a number of noxious gases with great propriety could be grouped rather with the intoxicants than with the asphyxiating agents, although by consent and without impropriety they are usually discussed with the latter.

Therefore with these considerations in view and for the purpose of limiting the definition to the convenience of legal inquiry, asphyxia may be stated to include merely the general results of mechanical interfer-

ence with the entrance and exit of air to the lungs and the prevention of interchange of the respiratory gases between the pulmonary air-spaces and the blood.

Within the limits of such a definition death from asphyxia may be considered as embracing death from strangulation, death from choking, and death from suffocation, including intoxication by certain deleterious gases. Much latitude is permitted in the use of these terms by modern lexicographers, but in the present discussion they are employed with definite significance. By the term *strangulation* is meant to be understood the interference of the passage of air to the lungs by external compressing force applied to the throat or neck, as in hanging or throttling. *Choking* should be understood as applying in those cases in which interference with respiration has resulted from obstructing agencies within the air-passages, such as foreign bodies, false membranes, strictures or tumors of the air-passages; or the presence of neutral or irritating gases or fluids interrupting the movement of the respiratory air to or from the lungs mechanically or by producing spasmodic constriction of the walls. The term *suffocation* may be employed to include all mechanical influences applied externally elsewhere than about the throat in the prevention of respiration; and may, for convenience, be required to include the results of those agents which, through their toxic influence upon the blood, render it unfit for convection of the respiratory gases. In this sense suffocation would be properly applied in such cases in which the mouth and nostrils are closed by some external substance, as a pillow or a mass of mud (often spoken of as *smothering*); where the respiratory movements are prevented by the pressure of a crowd or of a weight upon the chest; or where, as in poisoning by carbon monoxid gas, the hemoglobin of the red blood-cells is no longer able to enter into combination with the oxygen of the air or carbonic dioxid of the tissues. Moreover, here should be classified the rare cases of respiratory prevention from rarefaction of the surrounding atmosphere and confinement in a close space. It is unfortunate that clearer definition of the various terms applied does not exist, the confusion having probably arisen with the gradually appreciated insufficiencies of the words. Thus the term *choke*, from its etymologic relation with the words *cheek* and *chew*, was evidently at first applied to obstructions occurring in the mouth or upper part of the throat; while the word *suffocation* seems to have been later applied to instances of respiratory failure arising from causes operative below the level of the fauces (*sub, faux, -cis*). These original meanings having little value in the present state of our information, there is no necessity in trying to resuscitate them; and it seems better to attempt to define the terms according to the prevailing ideas, even though such definitions are somewhat artificial.

General Features of Asphyxiation.—Asphyxiation may occur either gradually or with greater or less suddenness. Gradual asphyxiation is commonly encountered in natural death from various diseases, while the rapid form is met either in death from disease or in accidental

or purposeful death. The gradual oncome of asphyxia, which may occasionally give rise to legal questions in circumstances of death from confinement in insufficient closed space, is marked by a general sense of discomfort, muscular weakness, nausea, headache, profuse perspiration, lividity of surface, rapid or slow weak pulse, labored respiration, loss of consciousness, development of anesthesia, death; the heart-beats persisting for an appreciable period after respirations have ceased. When the cause of asphyxia is most sudden, as is usual in legal cases, there is immediately after the application of the asphyxiating cause a brief period of quiet, lasting only for some seconds, the time the individual is able voluntarily to suspend breathing; then more or less violent efforts are made for several minutes to recover air, after which unconsciousness and insensibility come on and the respiratory efforts grow more and more feeble. Finally all respiratory movements are stopped after several minutes more, the heart-beats continuing a minute or two longer. Death is not regarded as having occurred until all cardiac pulsation has ceased, and it is possible to resuscitate the victim at any period until cessation of circulation has taken place. The countenance usually becomes livid and cyanosed, the eyes are prominent and widely staring, and there are a sense of fulness to bursting in the head, roaring in the ears, and dizziness; for a moment thoughts and recollections of a lifetime crowd in upon the mind, and then quickly die away into unconsciousness. The whole process may be completed in the course of four or five minutes, or may be protracted for two or three times as long. Occasionally asphyxia terminates life almost instantly.

Variations in the period requisite to destroy life may depend upon such factors as age, constitution, degree of oxygenation of the blood at the beginning of the process, and the degree of prevention of respiration, as well as the implication of the nervous system and circulatory apparatus by the active cause. Thus newborn infants may fail from several causes to breathe for a number of minutes after birth, and in fatal cases of congenital asphyxia pulsations in the funis may persist for fifteen or twenty minutes. Vigorous individuals and those possessing unimpaired circulatory and nervous apparatus, as a rule, endure asphyxiation for a longer time than the weak and ill, although the difference is rarely great. Yet such a feature should be thought of in cases involving inheritance by order of death, several persons dying from asphyxiation under the same conditions and together (see chapter on Sudden Death). The first period of asphyxiation may be lengthened, although to an unimportant degree, by the fact that immediately prior to the stoppage of breathing the blood had been well oxygenated by a number of strong, full inspirations; or, on the other hand, may be shortened if the respirations just preceding stoppage have been incomplete.

The length of time required in gradual asphyxia from confinement in close quarters cannot well be indicated, inasmuch as it is entirely dependent upon the amount and purity of the confined atmosphere at

the time of inclosure, the permeability of the inclosing walls to air, and the rapidity of oxygen consumption by the individual—this last factor resting upon the size of the person and the rate and fulness of respiration as determined by muscular effort or quiet, by health or disease, etc. In estimating the time in any particular instance it should be remembered that an average human adult will vitiate for continued breathing about 175 cubic feet of air an hour, and that double the degree of such vitiation may give origin to fatal asphyxiation.

While there are some special differences in the postmortem appearances in the different forms of death by asphyxiation, in general there is considerable uniformity. Usually there is lividity of the surface, especially about the face and upper extremities; the right side of the heart is engorged, the blood dark and uncoagulated, the various viscera are congested, and occasionally there are small patches of hemorrhage in different situations from the excessive passive engorgement. The lungs are often engorged and marginal emphysema frequently exists. There are various local signs, differing according to the mode of asphyxiation, which are to be sought for as evidences of the particular manner of production; and both general and local signs are subject to variation by a number of possible factors. In the examination of a body dead from asphyxiation, in addition to the recognition of the general mode of death, constant and great care is to be exercised in the discovery of such evidence as may be given by the body and the surroundings upon the particular mode of production; and the coexistence of pathologic conditions capable of causing death naturally by asphyxia and the careful estimation of their importance and influence are questions certain to arise in any legal proceedings upon the subject. The symptoms of asphyxia may be summed up as being due to an excess of carbon dioxid in the blood and the tissues due to insufficient oxygenation. The carbon dioxid causes constriction of the arterioles, thereby increasing cardiac labor, and reflexly stimulates and finally exhausts the respiratory center.

I. DEATH BY STRANGULATION

Death by strangulation is the fatal result of compression of the fauces, larynx, or trachea by any force externally applied to the neck. While such cases do not properly belong here, in this category are also included cases dead from nervous or circulatory lesions produced in the attempt, as may occur in hanging, where apoplexies from compression of the veins of the neck or serious mechanical injury to the cervical cord from "breaking the neck" are not infrequent. This form of producing asphyxiation includes those cases where throttling by the hand and compression by some encircling band about the neck, as the garrote of the Spanish, the bowstring of the Turks, or a cord or cloth, as used by the thugs of India, have been the methods of destruction, as well as hanging, where, the neck being partially or completely encircled by a band suspended from a superior fixed point, the weight of the victim's body is in more or less suspension.

1. Death by Throttling.—Throttling by the hand is practically always a criminal, murderous form of asphyxiation. It is not absolutely impossible that violent application of the victim's hand, even for a brief time, to the throat, as possibly in paroxysms of epilepsy or hysteria, might give rise to fatal after-effects or be immediately fatal; but such cases are practically unknown. Even where, in such cases, the hand is found applied to the throat and bruise-marks from the force of the constriction are evident, rarely can these be regarded as of particular importance, since, as a rule, throttling requires a continuous force for some minutes at least—almost an impossibility under any circumstances in the situation in question by the victim himself. When strangulation of this variety is accomplished by means of a constricting band, it is usually a purposeful act of destruction by an individual other than the victim, but instances of suicide by throttling in this way are common. Accidents, the result of foolish constriction of the neck and from excessively tight clothing, have occasionally occurred. Strangulation by throttling from the pressure of some hard substance against the throat is not unknown. In such instances a person has, perhaps, fallen senseless or stunned and lies with the throat across the edge of a board or rock, or some unyielding material of moderate weight has in some way been placed across the front of the neck of an unconscious person. Sometimes, where a band is applied about the neck of the victim for the purpose of murder, a knot in the ligature or a stone in the folds of the cloth is adjusted directly over the windpipe, in order that the compression of the walls of this passage may be more thoroughly accomplished in the act of constriction.

In throttling by the hand one or both of the murderer's hands are applied to the front of the throat, grasping and compressing the trachea, larynx, or the upper border of the latter. When both hands are used, frequently the application is such as to bring both thumbs of the criminal on the same side of the victim's throat, thus leaving but two marks on one side and a number of finger-marks upon the opposite side. In these cases the superficial injury to the tissues, more or less clearly defined bruise-marks, is found in a limited area not higher than over the thyroid cartilages, and the weaker pressure of the third and fourth digits makes little impression, as the upper part of the throat receives the compression of these less powerful constrictors. Or, the criminal directly anterior to the victim—as, for instance, when kneeling on the chest or abdomen and throttling at the same time—the thumb-marks are upon opposite sides of the windpipe, and the uppermost injuries are apt to be high up along the throat. Injuries to the back of the neck may also be produced, one hand being applied posteriorly, the other anteriorly, in order to accomplish compression more thoroughly. In very many instances the murderer has but one hand engaged about the throat, and one level receives the injuries from compression, the struggles of the victim demanding the use of the other hand for various purposes. Even when the bruises are seen all along the throat, however, only one hand moved from time to time may have been engaged. Usually in

throttling by hand, unless the victim has been very helpless from childhood, age, disease, or from being bound, other marks of violence will be found, as it is extremely difficult for the criminal to accomplish the act of strangulation by hand on account of the struggles and opposition of the person assaulted. In this form of throttling the backward and inward pressure of the compressing hand does not so certainly produce obstruction of the jugulars, and the degree of congestion of the face and brain is here usually less marked than in other forms of strangulation.

Throttling by means of a constricting band is practised in a great variety of ways and with various materials. The Turks use a strong bowstring in judicial executions, twisting it about the neck and thus producing a deep and thorough constriction of air-passages and blood-vessels in a comparatively short time. The steel collar, or garrote, used by the Spanish, produces its effects in the same way, although the area of compression is larger here than where a small cord has been employed. A broader band, made by the folding of a piece of cloth, has been successfully used for murderous purposes in the same way by the thugs of East India and other criminals. It has the advantage of leaving little postmortem sign of injury to the superficial parts of the neck.

Women have been known to strangle themselves with their hair; straps, ropes, wrapping-cord, neck-cloths, suspenders, and a host of similar substances have been in this or that case used suicidally or homicidally. In suicidal strangling by this method the ligature is, of course, found about the neck, sometimes fastened by a hurried knot or partial tie, sometimes merely wrapped tightly several times about the neck. In homicidal throttling by ligature the latter is not so uniformly found, the criminal often seeking to conceal the mode of death. A handle of wood is, perhaps, especially in suicidal cases, found twisted into the ligature, as in a hand tourniquet, in order to give an easy purchase in producing the constriction. Pieces of stone, wood, or other solid material may be found in the constricting band. They are applied directly over the air-passage and insure more thorough compression; or knots are sometimes tied in the ligature and applied in the same way for the same purpose.

Symptoms.—Occasionally, probably by the suddenness and force of compression upon the pneumogastric nerves, death occurs immediately in throttling by cardiac inhibition. The pre-existence of cardiac disease doubtless favors such a *dénouement*. Usually, however, a number of minutes intervene before the victim dies, and a number of symptoms generally occur, as already outlined. Violent struggles are, of course, always attempted in homicidal throttling, and only a greatly superior force of the assailants or some precaution, as binding the arms and limbs or the production of stupefaction, can prevent the evidences of these struggles.

In suicidal throttling the patient, while the ligature is being applied and fastened, is quiet for a few seconds, but quickly violent efforts to breathe ensue. Unconsciousness, preceded by great fulness in the head, lividity of the face, a roaring in the ears, and bulging of the eyeballs,

quickly comes on, thus preventing the self-relief which otherwise would in a large number of cases be applied effectively. During these few moments it is said the mind is very active. The same phenomena unquestionably occur in homicidal throttling. After a few violent respiratory efforts, as unconsciousness comes on, the respirations become progressively weaker and more and more irregular, and usually stop after four or six minutes. A few irregular efforts to gasp may be noticed, however, as much as eight or ten or more minutes after the compression has been applied. The heart at first becomes suddenly rapid and violent, but quickly loses its force and gradually subsides; the heart-beats, however, may persist a number of minutes after the last respiratory efforts. In a very few minutes after constriction of the neck, if the least possible amount of air can pass, the constriction, small râles may be heard in the trachea. Gas and solid matter may be passed by the rectum in the struggle of the patient; urine may be voided. The genitals are apt to become turgid, and sometimes semen is discharged; usually, however, the semen is discharged only into the urethra, and later than during the struggles of the victim, often probably by the rigor of the walls of the seminal vesicles just after death. Hemorrhages from the nose and ears may sometimes result from the venous fulness of their vessels.

Postmortem Appearances.—The body usually becomes rigid quickly, although this partly depends upon the amount and violence of struggling through which the individual has passed. The face is usually swollen, the eyes are bulging and partly open, the tongue is swollen and protruding or between the teeth; the countenance is livid; there is post-mortem lividity in dependent parts and arms. On opening the body the blood is found dark and fluid, present especially in the right side of the heart and in the veins. The right heart is distended, the left usually contracted, if examined early, but later relaxed. The state of the lungs seems to depend in a measure upon the amount of air contained. Before removing these organs, and in fact before opening the chest, in order to preserve as well as possible the pulmonary condition, the trachea should be dissected out below the point of compression and tied. Sometimes these organs are found comparatively bloodless except in the larger vessels, which contain the same dark fluid blood as the veins; and often a condition of emphysema about the borders is encountered, probably the result of the violent efforts at expiration. In the bronchial tubes and trachea there is often a small amount of bloody mucus and froth, or there may be small punctate hemorrhages in the tissue. In other cases, especially where the lungs contain less air, they are found highly congested. Small interstitial hemorrhages, usually of a stellate shape, are often found in the pericardium and pleuræ. The abdominal viscera are usually deeply congested, and there are frequently seen small subserous hemorrhages or hemorrhages into the mucous membranes of the stomach and intestine. The brain and cord may be much congested, and, especially when the jugulars have been much compressed, may contain areas of meningeal or parenchymatous hemorrhage. Con-

junctional suffusions often exist. Sometimes, especially where one or other or both the jugulars of both sides have escaped much constriction, as may happen in throttling by the hand, or where the compression is soon released, the amount of facial swelling and lividity and cerebral congestion is apt to be insignificant.

The position of the tongue depends in part upon what level of the neck receives the force of compression and how that compression is directed. As stated by Maschka, if the compression is applied high up above the hyoid bone, the tongue is forced into the back part of the mouth. If the pressure is below the hyoid bone, the tongue, however, will protrude between the jaws unless the compression has a decidedly downward direction, when its position is apt to be normal. Of greatest interest are the marks of violence upon the throat. These marks are those resulting from the bruising and capillary laceration caused by violence. When the strangling has been performed by a murderer's hand, these marks show as dark-bluish or brownish blotches following the outline of compression by fingers and thumb. They occur at different levels, as a rule, on the two sides of the throat, that of the thumb generally being a little higher than those caused by the fingers. On dissection a greater or less amount of blood and tissue laceration is found in the structures immediately underlying these areas. When the compression has been effected by a ligature, a line of depression corresponding roughly to the width of the constricting band is found, but where a soft broad ligature is used, as a cloth, this may be missing; again, if the ligature is removed before life is quite extinct, this depression is likely to be but slightly marked. This line is usually marked by ecchymotic patches, which are, however, less likely to be present if there has been no violence exerted in the application of the compression; and many look upon the presence of such suggillations as evidence of violence. This line is generally disposed horizontally about the neck, in contrast with the diagonal direction of the similar line in case of death by hanging.

If there have been very deep depression and excoriation of the skin by the ligature, this line becomes peculiarly dry, hard, and parchment-like several hours after death, and is very characteristic in such cases. On dissection of the injured parts muscular and connective-tissue laceration, hemorrhagic infiltrations, condensation of the soft parts from compression are usually found, and it is not infrequent that fractures of the hyoid bone or of the thyroid cartilages or similar injuries to the other harder structures in the vicinity are present. It is of note that this area of local injury is likely in marked cases to persist for a very long time in a recognizable degree; and in the celebrated Houet case, in Paris, served as an important part of the evidence to the conviction of the murderess eleven years after the death and burial of the victim.

In the determination of cases supposed to have perished from strangulation by one or other form of throttling the first effort is to be made to establish the actual fact of such mode of death, and thereafter to detect whether such strangulation has been homicidal, suicidal, or

accidental. The absolute determination of the former proposition is by no means a simple one, since the signs upon the body may all be more or less modified by circumstances.

The comparative value of these signs is variously regarded by different writers, and the combination of existing signs should be the basis of opinion rather than the degree of presentation of this or that particular appearance. Thus, while the existence of marks upon the neck is of unquestionable value, it must not be neglected that death by strangulation may have been accomplished without their production, and that, on the other hand, they may have been produced accidentally by the patient's own hand or by the impact of some hard substance against the neck upon which the patient may have fallen in a fit or otherwise, or may have been produced postmortem. While, when considered with the other features of the case, the dark, fluid blood, the congested condition of the lungs, the presence of emphysema of the lungs and of hemorrhages in different situations are of much importance in the general estimate, it must not be forgotten that these are possible in various forms of asphyxia and that they may be closely simulated by natural disease. The presence of signs of violence in other parts of the body than the neck, too, is of much importance, since it is quite possible that before the application of the ligature the victim was rendered insensible by a blow upon the head. Marks of violence also are found in such cases about the chest or abdomen, fractures of ribs, bruises of the chest and abdomen, or injuries to the abdominal viscera, the result of kneeling upon these parts in order to hasten the asphyxiation. In the absence of other lesions capable of accounting for death naturally, and in the presence of surrounding circumstances of corroborative nature, the absence or incompleteness of this or that appearance usually regarded as significant is of minor importance; and, conversely, the utmost caution should be observed in any absolute statement if there exist the least demonstrable possibility of death from natural influences, or if no outside evidence is found in confirmation of the suspicion of death by throttling.

Where, however, there is both external and bodily evidence of death by strangulation, further inquiry as to the exact mode is necessary, whether by hanging or by one of the modes of throttling. The mere discovery of a body suspended does not affirm that death occurred by hanging, although with the general appearances corroborating, such a supposition is reasonably tenable. The position of the ligature about the neck and the direction of the line of depression constitute the most important elements of evidence in differentiation of these modes of destruction, the ligature and mark of the same having a horizontal direction in case of throttling, while in ordinary hanging these present an oblique disposition, extending from point of lowest contact upward and about the neck to the point of adjustment of the suspended loop. In many cases, too, the greater violence done to the tissues, the parchment-like appearance of the skin in the line of depression, the marked ecchymoses along this line, the rupture of the cervical muscles, particularly the sternocleidomastoid, the rupture of the inner coats of

the carotid arteries, the fracture of vertebræ or their dislocation, speak clearly for death by hanging. Yet it should be remembered that in cases of suicide by so-called "partial suspension," if the ligature has been sufficiently soft and broad, and a comparatively small part of the body weight actually suspended, or the constricting band from adjustment and position of the victim be in a horizontal direction, nothing save the circumstances surrounding the case can serve to differentiate. Moreover, after the individual has been killed by throttling, perhaps with little or no sign remaining to indicate the mode of destruction from any other form of asphyxia, the body may be placed in such position and surroundings as to indicate quite a different mode of destruction. Thus, as cases exist on record, a body dead by throttling may have been immediately suspended, marks upon the neck being capable of production within half an hour to an hour after death so as to be identical with those ordinarily produced by hanging. Under such circumstances the idea of suicide may be with difficulty avoided; and only the greatest care in recognition of evidence in the surroundings and of marks of violence upon the person of the victim incompatible with suicide by hanging can serve to present competent testimony of death by other than suicidal means.

In endeavoring to determine the question of suicide or homicide in those dead from throttling the character and severity as well as the position of marks of violence upon the neck and elsewhere should be regarded, and, too, the presence or absence of a ligature about the neck, as well as the simplicity or complicated manner of its application and fixation. Finger-marks alone upon the throat of a body, without the sign of the use of a ligature, if accompanied by the internal evidence of death by asphyxia and by injuries to the deeper structures of the throat, may be looked upon as strong evidence of murder, since it is not probable that sufficient violence to the neck could be self-inflicted to produce the deeper lesions about the throat. Yet even where the condition of the blood and heart and other viscera indicates asphyxiation, mere finger-marks upon the surface unsupported by deeper injuries may have been produced by the victim himself, either consciously or unconsciously.

When throttling has been due to a ligature, the nicer degrees of adaptation of a knot or inserted hard substance to the trachea or larynx of itself speaks rather for the case of suicide, the haste and perturbation of the murderer more frequently preventing careful adjustment. Suicides by this method may show some measure of failure properly to fix the ligature on account of oncoming unconsciousness or loss of presence of mind. The use of a small stick or similar object as a tourniquet windlass after comparatively loose application of the ligature has frequently been encountered, the twist being prevented from becoming free by the stick locking against the ground or person of the suicide. In homicidal throttling by ligature undue force is likely to be applied in various ways, and injuries of different forms inflicted in different parts of the body. From violence of application of the ligature or

from jerking or wrenching the neck by means of the ligature, the parchment-like skin in the line of depression, ecchymoses along this line and the more serious structural changes of the deeper parts are likely to be found, and hence these are indicative rather of murder than of suicide.

There is usually little difficulty in the determination of this question, however; and in cases where the evidence of throttling is sufficiently clear to establish this mode of death, rarely are signs wanting to classify it as homicidal or suicidal either upon the body or in the surroundings and general testimony. A much more difficult task is the detection of those cases where the throttling has been skilfully done with a broad soft ligature and the ligature immediately removed. In some instances all that can be said is that death has resulted from asphyxiation; and apart from extrinsic testimony, no positive decision as to the mode of its production can be given. The careful exclusion of every appreciable natural cause in such cases is, however, of considerable value, and if associated with sufficiently corroborative evidence from the surroundings, general testimony may serve reasonably to establish murderous guilt. The absence of superficial marks of violence should not deter the examiner from careful dissection of the deeper structures of the throat, since serious lesions of these parts may exist without any external sign.

Accidental throttling is rare, but death has been known to occur thus. Excessively tight collars or neckbands, the entanglement of neckties in moving machinery, the slipping of some band sustaining a weight upon the back from forehead or shoulders to encircle the neck, the foolish application of constrictions about the neck for purposes of show, the compression exerted by the edge of a bedboard upon the neck while the head hangs over the side, and similar modes of production have been capable of terminating life in occasional instances.

Among the natural causes of death liable to misinterpretation and confusion with the foregoing, apoplexies are perhaps the most important, inasmuch as several such cases have led to legal action on the supposition of strangulation. The fact that the intense cerebral congestion in strangulation may give rise to apoplectic effusions in the brain makes the difficulty of diagnosis all the greater; yet the general rule that such apoplexies are more liable to occur the severer the force of compression about the neck will, in most instances where the external testimony permits, relieve the suspicion if marks of such violence be absent from the dead body. The condition of the blood and internal viscera will, moreover, serve in most cases to render the decision more easy, since in ordinary apoplexies the blood is not fluid and there are often lesions of the heart and vascular changes of greater or less importance. Death in profound alcoholic or opium narcosis may likewise mislead, and should carefully be excluded.

2. Death by Hanging.—This is a form of strangulation where the more or less completely suspended body of the victim by its weight exerts the force necessary to compress the structures of

the neck against the fixed ligature encircling it, and thus produce respiratory obstruction. As a matter of fact, death by asphyxia does not always occur in hanging. Cerebral congestions or apoplexies, injuries to the cervical cord or to the pneumogastric nerves are sometimes produced in the process and may cause death. In the majority of cases, however, asphyxiation is the mode of oncome of death. Hanging is in many of the states of this country and in many other lands the judicial method of terminating life. It is a frequent method of self-destruction; is often employed homicidally, especially in "lynching"; and occasionally is accidental.

In *judicial hanging* the doomed individual is caused to stand upon a trap-door in the floor of an elevated stage or scaffold; the arms and limbs are pinioned; sight is prevented by a cap over the face and the noose or loop of a rope is placed about the neck. The rope selected should have been tested to prove its strength, and for advantage should be rather pliable and elastic. Its upper end is firmly attached at a variable height above the head of the criminal about to be executed, and sufficient length allowed to permit a fall of the body of from 1 to 10 feet, usually 5 or 6 feet. The length of the "drop" is usually arranged in inverse proportion to the weight of the victim's body. The adjustment of the loop has been the subject of considerable discussion. It is usually drawn comfortably tight about the upper part of the neck, and so arranged that the knot is placed just below and behind one ear. Sometimes, however, the knot is adjusted to the back of the neck; and where it is desired to "break the neck" of the criminal, it is arranged anteriorly beneath the chin. These preparations complete, the trap-door upon which the culprit stands is allowed to fall, and the body of the victim drops to the length of the rope.

If the knot has been properly arranged, the drop of sufficient distance, and the suspended body of a sufficient weight, death may occur at once from injury to the spinal cord or medulla by dislocation of the vertebræ or fracture of the odontoid process of the axis. No exact estimate can be given of the frequency of such occurrence, since, for its production with any uniformity, it requires that special provisions shall have been taken. In order to accomplish this end the knot should be large and adjusted close to the neck on the side or beneath the chin, and the drop should be as long as possible, 10 feet being recommended by Houghton. Immediate death occasionally may ensue from the sudden sharp pressure upon the vagus nerves, because of the complete and rapid inhibition of the heart.

Congestive apoplexies or occasionally true effusive apoplexies may operate to destroy life more rapidly than is usually the case in asphyxiation alone. In the majority of cases, however, death occurs from asphyxia or from asphyxia associated with one or more of these other possibilities, and requires from eight to twenty or more minutes after the victim has fallen. When death is immediate, the body, except for a few slight muscular quivers, hangs motionless, the head fallen over to the side opposite the knot and the neck looking unusually long. In

the ordinary cases, where asphyxiation plays the major or only part in destroying life, there ensue the usual stages, as described in strangulation by any form of ligature, except that from the violence of the fall the first stage is usually not of active and exalted consciousness, but of immediate unconsciousness. Occasionally, however, it is probable, from the experience of a few of those rescued before death was complete, that the same mental activity, the same crowding of past events into the memory for a second or two, does take place. As soon as the drop has fallen the body, for a few seconds to a minute or more, hangs limp and quiet; then convulsive movements take place, persisting for two or three minutes. These are: drawing up of the arms and limbs, clenching of the hands, heaving of the chest, and other contortions made in the efforts to respire. These soon disappear, except that possibly some minutes later slight respiratory efforts may be noted or muscular quiverings be manifested here and there. For the first few seconds the face is pale; then, as the convulsive movements occur, it becomes more and more deeply livid, and little blotches may occur beneath the skin. The face becomes swollen; the eyes bulge; the mouth hangs open; the tongue shows between the teeth; free salivation is likely to occur, and the saliva drops from the corners of the mouth. Slight bleeding from the tongue, where it has been bitten by the early convulsive movements of the jaw, or from the nose, on account of venous congestion, may appear about the face. The external genitals are likely to become turgid; urine and feces or gas may be voided; occasionally there are discharges of genital fluid, although this is not uniform or complete, and probably is not accompanied by erotic feelings, as has been claimed. The pulse is at first quick, hard, and full, but rapidly loses in force, fulness, evenness, and disappears a few minutes after the closing of the convulsive stage. The heart-beats persist for a longer time, however, becoming more and more feeble and irregular, and finally, after ten or twenty minutes from the beginning, they cease, and death is complete.

The first stage is one of quietude, consciousness being possible; it lasts, as stated, for from but a few seconds to about one or one and a half minutes. It is succeeded by the stage of respiratory effort and convulsive movements, lasting from two to four or five minutes. Unconsciousness is invariably present after a few seconds of this period. The third stage is one of almost absolute quiescence, marked by but few and feeble efforts at respiration; the heart continues to beat, becoming progressively weaker and weaker. With the cessation of circulation this third stage is complete and life is extinct. The third stage is usually longer than both the others, often lasting twelve or fifteen minutes.

Homicidal hanging, as in lynching, is often very similarly performed, the drop being accomplished by the sudden removal of some elevated support, upon which the victim has been standing. Thus after the adjustment of the noose and the fixation of the rope to a limb of a tree or some similar object above the level of the victim's head, the

chair or box on which the unhappy wretch has been standing may be kicked or jerked from under his feet, or the cart upon which he has been supported is dragged away. In all such cases, as a rule, the length of fall is small compared with that in judicial hanging, the chance of breaking the neck is comparatively slight, and death generally occurs by asphyxia. More often in lynching the victim is drawn up by the neck from the ground and held suspended until death has taken place. Breaking the neck by this method is almost unknown, and the absence of the violence of the fall results in slighter local damage to the cervical structures generally.

Suicidal hanging may resemble judicial hanging, but there is rarely much drop. The individual, after adjusting the rope and noose, may jump from a table, a chair, or other object upon which he was standing, or, suspended by a short rope, may kick such an object from under his feet. Frequently, in case of suicide, suspension is only partial, the body being found after death with the feet touching the floor or ground, or in a kneeling posture, sitting, or even lying prone, with only the head and neck in suspension. The point of fixation of the ligature, moreover, may be entirely insufficient to support the weight of the body, a clothes-hook or nail partly driven into some support being perhaps employed. Very slight ligatures also may be used in these cases of partial or incomplete hanging, as thin twine or cord, pieces of clothing, neckties, suspenders, stockings, strings of shirts, or similar substances. Bodies may occasionally be found half supported by the ligature, half leaning against a wall, with perhaps only a thin bit of twine encircling the neck and insecurely attached above the loop. Usually in these cases the hands are quite free, and only an indomitable will or the rapid loss of consciousness and physical control could prevent frequent withdrawals from this practice of suicide after it had been begun. The latter is probably the better explanation of the almost universal success. Sometimes, however, fearful of involuntary self-interference, the victim has bound his hands, using his teeth to aid in fastening the knot; such a precaution is, however, quite rare, and is unlikely to add much to the perplexities of the case, as the position of the pinioned hands in front, rather than behind, the body, and the general appearances of the knot should indicate its application by the victim rather than by another.

As a general rule, death from suicidal hanging is one of pure asphyxiation, the comparatively slight violence of these cases rarely giving rise to the severe injuries of the cord and spinal column or other important cervical structures liable in cases of judicial hanging. Syncopal attacks with fatal termination from compression of the vagus and disturbance of the circulation by the ligature do, however, frequently occur.

Accidental hanging is very rare. Children playing in swings or with ropes may occasionally become entangled in such a way that strangulation occurs. One now and again meets instances of where a child slips from a fence, and, in falling, has its neck caught between the upper

ends of the palings, with the result of death by suspension if not at once relieved. In play and in public show persons have been known to be suspended partially or completely; and accidents have now and then taken place under such conditions. The circumstances here are usually so complete that only the most formal inquiry arises and there is rarely opportunity for implication of the living in any principal part.

In all these varieties of suspension the phenomena occurring in the course of the process are identical with those of judicial hanging; or, in the case of partial suspension and suspension without a drop, with those of throttling by ligature. When there is a decided fall of the victim, with the sudden jerk of the rope about the neck consciousness may be destroyed at once, and probably is destroyed in a large number of cases. The body is motionless, as if stunned; and it is the testimony of a number who have been rescued immediately that they possessed absolutely no recollection of the hanging. If consciousness is not at once destroyed, as is usual when there is no fall, a moment or two of quietude intervene—the natural period during which the breath may be held. The head feels full and almost bursting; the ears ring and roar; there is a feeling of bodily lightness; the activity of the mind is greatly increased, and the whole life seems to pass in review in the second or two of consciousness. A feeling of necessity to breathe becomes more and more imperative, and desperate efforts are made, but without success. Unconsciousness now comes on quickly. The first stage of quiet passes abruptly into that of convulsive, irresponsible, involuntary efforts at respiration, lasting, as indicated, for several minutes, and identical in all its details to the convulsive stage of judicial hanging. The last stage, also, characterized by the persistence of the heart's action alone, is the same as the final stage of legal executions.

Many of the phenomena encountered in the process of hanging are subject to variation depending upon circumstances of compression. Thus, while typically the face becomes cyanosed and swollen from interference with the venous circulation through the jugulars, a considerable proportion of individuals present a pallid countenance. This is especially likely to be the case when death occurs quickly from cardiac syncope, from compression of the vagi, or from the added influence of co-existent cardiac disease. The rapid failure of circulation in such instances gives little opportunity for the accumulation of any marked excess of blood in the head and face. So, also, when the adjustment of the loop and attachment of the ligature leaves one side of the neck free from compression, the unimpeded venous channels of such an area carry off the blood as rapidly as it can be brought to the head through the partially constricted carotids. In judging of the influence of compression on the vessels of the neck, most text-books lay too much stress upon the production of an anemia of the head and face by compression of the common carotid arteris. Both from their more exposed position and their less resistant walls, the jugular veins, superficial and deep, must be more readily and more completely obstructed by the compression of a ligature about the neck, and when

the compression is sufficiently serious to narrow the arterial flow, the venous return must be more impeded. It is, therefore, natural that in all cases where there is deep compression of the neck, if the circulation does not at once and completely cease, there should accumulate through the vertebral arteries and smaller deep collateral circulation a considerable excess of blood in the venous and capillary vessels above the ligature. Thus a pallid countenance can exist only where this venous circulation is, at least in part, free, or where there is absolutely no further access of blood by the deep and unobstructed arteries of the neck, as may be expected, for instance, when death has occurred from syncope. Moreover, the protrusion of the eyeballs and conjunctival suffusions which frequently occur are often absent, dependent largely on the same cause. The swelling of the tongue, noticed especially about the base, is subject to similar variations for the same reasons.

The rapid onset of unconsciousness is frequently ascribed to a cerebral anemia from compression of the carotids, but it is rather to be referred to cerebral congestion of a passive form and to the carbonization of the unaërated blood passing to it through these incompletely compressed arteries and the deeper and uninfluenced vertebrals. The mere fact, especially in those cases presenting pallid countenances, that autopsy often fails to show cerebral congestion of any marked degree is of little significance, since the fluid blood readily passes downward as soon as the constriction is released if the position is favorable. Marked capillary congestions about the lower part of the head and face and in the neck above the ligature are likely to persist without diffusion.

The position of the tongue is less frequently recorded as varying. Usually it is found protruding or between the teeth, but sometimes it seems rather retracted. This probably depends largely upon the position of the ligature and its line of traction. When the ligature is above or on the same level as the hyoid bone and the knot is well adjusted posteriorly, so that the force is directed backward, the root of the tongue is dragged backward in the pharyngeal space, and probably aids in respiratory obstruction. If the knot is placed more anteriorly, this line of traction does not exist, and the tongue is likely to remain in a relatively normal position unless forced outward by respiratory efforts. When the ligature acts below the level of the hyoid bone, its upward traction tends to force before it the structures about the base of the tongue and cause it to protrude to a greater or less degree.

As a rule, the face is more or less contorted during hanging, and may retain this appearance after death. Very often it is quite placid, an appearance likely to coincide with pallor of the countenance, although not invariably. The contortions are probably the expression of the respiratory struggles, and mark those cases in which asphyxiation is the particular mode of death; while if death follows the breaking of the neck in the drop or occurs in a syncopal attack, the countenance is naturally unmoved. It is difficult to explain why in some the hands should clench with intense force and in others remain with the fingers

extended, but such is the case. As a rule, the clenched hands are found in persons dying or dead from complete suspension; while it is more or less common to meet the hands quite open in incomplete suspension. The turgescence of the external genitals, the discharge of genital fluid, of urine, of feces, or of gas are symptoms commonly alluded to, but are by no means constant phenomena, and are not peculiar to death by strangulation. The lividity and swelling of the limbs and lower part of the trunk suggest that the partial genital erections met in these cases may be a part of the general hyperemia from gravitation.

It is impossible to state definitely any period of time necessary to destroy life by hanging. Life may cease from the beginning of the process or may persist up to half an hour. By using a fixed knot and loose loop, and adjusting the latter anterior to the ramus of the jaw and posteriorly high up along the occipital region, individuals, exhibitors mainly, have endured complete suspension for a much longer time; several accidents have taken place among such foolish exhibitors by the slipping of the knot, thus drawing the rope back over the respiratory passages and causing asphyxia. Resuscitation is improbable after the termination of the second or convulsive stage, and even in this stage the chances for recovery are always questionable. Yet so long as the heart continues its action it is wise to use every endeavor to recover, since patients have revived after some minutes' cessation of respiratory movement and several hours after the beginning of artificial respiration.

Postmortem Appearances.—In inspecting the body of one dead by hanging care should be taken to note precisely every circumstance and feature possible before the corpse has been disturbed. Evidences of a struggle, the manner of attachment of the ligature, marks of any kind upon the ligature or surroundings, the mode of adjustment of the loop, the probable length of the drop, etc., should all receive attention. The condition of the face, eyes, mouth, tongue, hands, limbs, genitals, and the clothing should all be inspected and recorded. Thereafter, the body having been lowered, inspection should be made of the condition of the neck and for marks of violence elsewhere upon the exterior of the body.

Many differences may be found in the character of the marks of the ligature. Usually there is a single line of depression, passing obliquely about the neck, most marked on the side opposite the knot, and entirely absent close to the position of the knot. When the position of the victim has been such that the force of suspension does not act along the line of the axis of the body, as is often the case in incomplete suspension, instead of an oblique line of depression the mark about the neck may be horizontal, as in throttling by a ligature. However, unless a slip-knot has been employed, the absence of the mark on the side of the neck corresponding to the knot of the ligature constitutes an important means of differentiation. In general, the looser the adjustment of the loop, the more oblique the line of depression. This line is deeper,

as a rule, along the sides of the neck, the opposition of the larynx and similar structures often preventing it cutting in so deeply anteriorly. It is usually less marked in fat persons than in those that are moderately spare. The weight of the body and the length of time of suspension, as well as the size and nature of the ligature, are important factors in causing the depth of the depression. If the loop has been a double one, the mark is also double, one portion having a horizontal and the other an oblique direction if the inner part of the noose be free to slip. Both lines will be oblique, however, if both strands are attached at the knot. In the former case the horizontal mark will be found to extend completely around the neck, as in case of throttling by ligature. As may be expected, the narrower the cord, the deeper the furrow of depression. As a rule, this furrow is pale at the bottom, and the margins are swollen and discolored.

When considerable force has been expended, as in hanging with a fall, suggillations along the bottom of the groove are often found; but these are not present, for the entire number of deaths by hanging, in as great proportion as in death by throttling. Instead of pallor along the bottom of the depressed line, if the suspension has been brief and little excess of force employed, the surface may look normal or slightly red in color. If there has been much excoriation by the ligature and the suspension has lasted for several hours, the skin in the bottom of the groove may have a yellowish-brown tint and a hard, dry appearance—the so-called “parchment-skin.” Even if not noted upon releasing the body from suspension, this last is likely to develop within a few hours after exposure of the groove to the air. The cyanotic appearance of the upper margin of the groove is almost invariable, usually appearing even if the body has been suspended shortly after death from some other cause. The cyanosis of the lower margin is usually less marked, and may be absent. Its presence is a fair indication that hanging was performed *antemortem*. Ecchymoses along the margin of the furrow are more common above the line of the ligature than below, but, except in cases of hanging with drop, are less frequent than in throttling. It is to be remembered that the appearance of this line of depression is a relative one, and that, in its appreciation, the length of fall and consequent violence, the weight of the suspended body, the duration of suspension, and the width and nature of the ligature must all be considered. Many cases, especially of suicidal hanging, fail to exhibit it at all; and, on the other hand, it may in a measure be produced by suspending the body within one or two hours after death.

When the body has been almost or completely suspended, the neck is distinctly elongated and pliable. This is not necessarily due to any vertebral fracture, but may result from the stretching of the intervertebral tissues.

Subject to variation, as already considered, the other external appearances are likely to be found as follows: the face is swollen, cyanosed, and blotched; the eyes are prominent and sometimes the seat of subconjunctival hemorrhage; the tongue is swollen and partially protrud-

ing; it may perhaps be bitten and bleeding; blood may be found emerging from the nose and ears. The hands and arms are livid and swollen, and the fingers may be so tightly clenched that the nails are found wounding the palms. The limbs and feet are livid and swollen; the genitals are large, and evidences of the expulsion of semen and urine may be encountered, as well as of the expulsion of feces from the anus. Hemorrhoids may be found prominent and bleeding. The time of appearance of rigor mortis depends largely upon conditions of bodily exertion prior to the hanging and the severity of the convulsive stage; as a rule, it does not come on for one or two hours after death, but may be immediate.

Dissection of the neck usually shows the tissues immediately beneath the ligature to be compressed and bloodless; but, as might be expected from the probable injury to the smaller vessels, when much violence has accompanied the process, interstitial hemorrhages of variable extent are found in and about the line of compression, just as in throttling by ligature.

In consequence of the violence of the fall lacerations are not infrequent. The sternocleidomastoid muscle is frequently the seat of such injury, and occasionally the inner coats of the carotid arteries are similarly torn. This laceration of the carotids has been ascribed to the force of compression by the ligature, just as in the ordinary surgical operation of ligation of an artery the inner coat is usually severed; the great difference of degree and completeness of compression, and the fact that these vascular tears are usually met below the level of the ligature about the neck and not upon exactly the same level, do not afford evidence of such a view, and render it probable that they are entirely the result of the sudden stretching force in the fall. Degenerative states, such as atheroma, favor the occurrence of such an accident. The extension of blood between the coats of the vessel wall at the place of rupture is to be regarded as indicative of the existence of circulation at the time of and immediately after the injury. In a small proportion of cases, dependent on the position of the ligature and the force occurring in the process, the hyoid bone is found broken, usually in its larger cornua. The thyrohyoid ligament may be found lacerated. Dislocations or actual fractures of the thyroid or cricoid cartilages are occasionally encountered; or, rarely, dislocations of the arytenoid cartilages. Occasionally, especially in judicial hangings, dislocations of vertebræ, with or without actual fracture, are found. Most frequently this obtains in case of the odontoid process of the axis or as a dislocation of the axis from the third vertebra. In either case, of fracture or dislocation or both, considerable damage is likely to be found in the surrounding tissues. These are often the seat of hemorrhage, and the membranes of the cord and the cord itself, by pressure and extension, are sometimes seriously lacerated. By transmission of the force occasionally a demonstrable injury is produced in the medulla. It is manifestly impossible to indicate any exact proportion of cases in which such lesions are encountered, inasmuch as the factors for their production vary with the

mode of procedure; they are, however, most frequent in judicial hangings, and occur but rarely in cases of suicide.

Upon opening the larynx and trachea the mucous membrane of these passages, particularly in cases of hanging with violence, is found suffused and reddened, occasionally lacerated, at and near the level of the ligature, and at times small hemorrhages are found upon the surface of the membrane. There is usually also a diffuse hyperemia of the entire respiratory mucous membranes, and there may be considerable mucous secretion upon the surface. When the strangulation has been incomplete, this mucus may be more or less frothy, from the partially successful efforts to breathe. The lungs are found in a condition similar to those seen in cases of throttling by a ligature, usually deeply congested, especially in dependent parts, sometimes emphysematous and comparatively free from blood. Ecchymoses beneath the pleuræ and hemorrhages into the tissues of the lungs are seen, but not so frequently as in throttling. The heart is usually distended with blood in the right side. The left heart is comparatively empty. When both sides contain blood, the inference is warranted that death took place from syncope rather than asphyxia. Subpericardial hemorrhages are not so frequent as in throttling, and, as a rule, the pericardial sac contains but little serum.

The blood, as in other cases of asphyxia, is usually found in the venous rather than in the arterial circulation, and is dark and fluid. There are few clots, and these are small, being found in the heart or elsewhere. The abdominal viscera are congested and dark in color. This appearance is more marked if suspension has been prolonged. The brain is usually moderately congested in the venous circulation, but rarely extremely so. Sometimes, however, it is highly hyperemic, and in a very small proportion of cases—less than 1 per cent.—actual hemorrhages exist. This relative absence of deep congestion is probably to be accounted for by the drainage of the blood after cessation of circulation into the face and neck, on account of the position of the head. In cases where death has taken place by immediate circulatory failure, corresponding with the pallor of the face in the same examples, the brain may be found actually anemic. It is possible that if the body has been lying with head lowered for a time before the brain is examined, some return flow of blood to its dependent parts may mask to some extent the real state.

Treatment of Strangulation.—In all cases of strangulation the plan of treatment is about the same. All impediments to respiration must be removed at once. If in suspension, the body must be released instantly, any ligature removed, and all constrictions about the neck or body by clothing loosened. Artificial respiration must be applied immediately, and it is often required to be continued for several hours. The stagnant circulation is best relieved by moderate blood-letting (up to 500 c.c.) and friction of the surface. Cardiac stimulants should be administered freely hypodermically; and stimulation of the sympathetic nerves by faradism or galvanism tried. Tracheotomy below the level of the compression should be performed if, from swelling of

the tissues or fracture or dislocation, much impediment to respiration exists. The heat of the body should be maintained by warm blankets, hot-water bottles, and the like. Resuscitation is rarely successful after respiratory effort has ceased, but the possibility of a favorable result remains as long as the circulation continues. Death not infrequently occurs many hours after temporary or apparent recovery, due to meningeal or pulmonary congestion and edema. In some cases the health of the patient has been materially and permanently impaired. Convulsions, paralysis, and mental disturbances have been noted to follow strangulation; these are no doubt due to circulatory disturbances in the brain or actual injuries to the cord contracted during the process.

Legal Considerations.—In but few cases where the circumstances and surrounding evidence agree with the postmortem appearances can a reasonable doubt as to death by hanging arise. Yet it must not be forgotten that a body suspended immediately after death may present many of the marks caused by hanging in life, and that such a procedure might be resorted to in order to prevent suspicion of other modes of destruction. Thus the furrow of compression by the ligature, and its dry, leathery appearance can unquestionably be produced, as proved by experiment upon cadavers, by suspension within an hour or two after death; and even the severer cervical injuries, as fracture of the hyoid bone or of the larynx, or fracture or dislocation of the cervical vertebræ, may likewise result from postmortem hanging. In such cases, from the recognition of external marks of violence, improbable from death by hanging alone, from the absence of decided hemorrhage about sites of lesions in the deeper parts of the neck from hanging, from the relatively uncongested appearance of the lower border of the groove of compression, and the failure of the usual internal evidences of asphyxiation, it is sometimes possible to affirm that suspension was performed after, rather than before, death. However, the value of the absence of the internal signs of asphyxiation fails in these cases when the cervical lesions point to a probability of immediate death from syncope after the drop.

Cases, therefore, may present themselves in which medical testimony alone must fail in our present knowledge clearly to establish one or the other side of this question. Often, however, the collateral evidence in relation to the mode of attachment of the ligature, or marks of various kinds (as blood-stains) upon the latter, or upon the person of the victim, or in the vicinity of the body, may supply the deficiency and render the problem reasonably clear.

The determination of death by hanging from death by other forms of asphyxiation, especially of other forms of strangulation, when the circumstances surrounding the body when discovered allow such question, is likewise often difficult. Here the special appearances about the neck constitute the most available means of distinction. The peculiar marks of the fingers and thumbs in the anterolateral regions, over the respiratory passages, when throttling has been performed by hand; the complete and horizontally arranged furrow from the ligature in throt-

ting by ligature are here of great import, in contrast to the usually oblique line of compression, often incomplete near the position of the knot, in death by hanging. As most cases of hanging with a drop of any length are instances of judicial execution, under other circumstances the appearance of suggillations in the groove and along its borders, interstitial hemorrhages in the deeper tissues beneath the line of the ligature or marked injury to the larynx and trachea must speak rather for the violence of murderous throttling than for ordinary suicidal suspension. Subpleural, subpericardial hemorrhages, submucous ecchymoses of the stomach and intestine, and cerebral apoplexies are more frequent in throttling and suffocation than in hanging; and marks of violence upon the body exerted to hasten death, as by kneeling on the chest or abdomen, are more likely to be found when death has occurred from throttling. Yet the entire absence of any mark upon the neck or elsewhere in either case must not be forgotten as possible, and collateral evidence therefore not neglected.

Aside from legal executions, hanging is almost always suicidal. Among suicides this method stands easily first—of 25,737 suicides analyzed by Briand and Chaudé, 11,608 are credited to strangulation by hanging and throttling. In a large proportion of cases the absence of any evidence implicating persons other than the victim, and the existence of testimony indicating more or less specifically that death was self-inflicted, relieve the necessity of further legal inquiry. When, however, questions arise, an answer may be possibly obtained in the condition of affairs in which the body is found, but not in any particular lesions in the body itself. Thus it would manifestly be impossible that a body found hanging with the arms pinioned at the back could have come into such a state without the interference of another person. A body found hanging freely, and without means at hand whereby the individual had ascended at least high enough to have adjusted the loop, must indicate, in the absence of strong conflicting external testimony, that another was implicated in placing it in such position. On the other hand, the inference in cases of incomplete suspension, in the absence of conflicting evidence, is of suicide, or, in rare instances, of accident. The absence of other evidences of violence upon the corpse or in the vicinity must further corroborate such a view, since it is scarcely possible that a homicide could be perpetrated by such means against the active resistance of the victim. The insignificance of the common cervical marks, especially of the deeper structures, is suggestive of suicide rather than of homicide; and in a large proportion of cases of suicide, with the exception, perhaps, of slight reddish discoloration beneath the comparatively loose ligature in incomplete suspension, they may be entirely absent.

II. DEATH BY CHOKING

By this term is meant to be indicated all cases of fatal asphyxia resulting from the occlusion of the air-passages by agencies within these passages or their walls. Such obstructions may be of external origin,

solid, liquid, or gaseous; or may arise within the body as the result of disease, as tumors of the larynx, croupous membranes, edema of the larynx or trachea. The latter group is essentially natural and of no especial concern to the legal physician, save in a negative sense.

For legal purposes, then, the foregoing definition may be modified so as to include only those cases of fatal occlusion of the respiratory passages as may be induced in one or other way by foreign agencies introduced within these passages. Such occlusion may be a direct mechanical plugging or filling by the foreign substance, or it may be the result of a laryngeal spasm or spasm of the glottis induced by the irritation from such an external substance in the course of its entrance into these passages. The compression of the posterior, yielding wall of the larynx and trachea by some large, hard mass in the esophagus is likewise commonly accepted as a form of choking, although differing slightly from true choking or occlusion.

(a) **Choking by Solids.**—Almost invariably in choking by a solid mass the occurrence is accidental. There are on record a few instances in which solid substances, as corks, handkerchiefs, dirt, and other matters have been forced into the back of the mouth or actually into the glottis with murderous intent; and suicidal individuals, especially those in confinement—the insane, for example—frequently attempt to take their lives by similar means and are occasionally successful. Even when not immediately successful, as the after-result of irritation of the epiglottis or rima glottidis by a foreign mass or by some caustic material which may have been taken into the mouth and swallowed, but prevented from destroying life directly by antidotes, serious closure from swelling of the tissues may endanger life or actually cause asphyxiation. Accidental choking may occur from the swallowing of too large and too hard a bolus of food, which, pressing through the wall of the esophagus, causes compression of the posterior respiratory wall, and may thus actually close the air-passages. Sometimes a mass of food too large easily to engage in the upper part of the esophagus overlies the epiglottis or the opening of the glottis and thus prevents inspiratory movement of the air. Or smaller bits of food may, especially if the epiglottis is destroyed or impaired by disease, actually get into the opening of the glottis and close it.

Nails, tacks, buttons, and a host of different small objects have been known thus to enter the upper respiratory tract, and sometimes, if their size permit, pass downward into one or the other bronchus, usually the right, on account of its straight direction and large size. Attempting to speak and swallow at the same time, or attempting to cry out when some small foreign substance, as a coin, is in the mouth; endeavoring to inhale while partially vomited matter lies in the pharynx: such conditions are especially liable to produce such an accident. From inspiration during vomiting the authors have known a lumbricoid worm to gain entrance to the larynx and destroy life by asphyxiation.

In feeding the insane through an esophageal tube with fluid or partially fluid food the possibility of inserting the tube into the larynx

instead of the gullet should be kept constantly in mind, as accidental asphyxiation is possible both from the tube itself and from the fluid which is poured through it after improper adjustment. Deplorable accidents of this sort have occurred in a number of asylums, and serious inflammatory after-results, such as inspiration pneumonia, have followed the entrance of very small quantities of such fluid food material. It should be remembered, also, that among the insane, especially with parietic dementes, careless habits of eating and more or less muscular inco-ordination in swallowing may, with unusual frequency, cause paroxysms of choking. Drug habitués, particularly ether addicts and alcoholics, have been known to choke on regurgitated food while in a semistuporous condition.

Children, from their frequent habit of placing various articles in the mouth in the midst of play and laughter, are frequently subject to accidental choking, a sudden inspiration drawing such objects into the larynx. The sudden sharp, full inspiration following a slap on the back may, if some suitable substance be in the mouth, cause its withdrawal into the respiratory passages. There exists during sleep or the unconsciousness of anesthesia or of an epileptic attack, especial liability for the entrance into the fauces of such material as may be in the mouth, and hundreds of different substances are recorded in medical literature as having thus given rise to choking of an acute or prolonged type. As examples may be enumerated such things as pieces of meat, potato, bread, or other food, pieces of nutshell, teeth, plates of artificial teeth, tooth-picks, bits of pencils, buttons, nails, coins, grains of various sorts, worms, flies, corks, etc.

Symptoms.—Immediately after the entrance of the foreign material, which, it should be added, may not be foreign, but have developed within the respiratory passages—as, for example, pieces of false membrane, a small tumor, or something of the sort—there occurs a more or less severe paroxysm. This may be fatal immediately, as is usually the case in instances requiring legal consideration; but the attack is often survived, only to give rise to subsequent paroxysms upon every change of position of the foreign mass, each with the possibility of fatal termination. Or a reaction of varying intensity, acuteness, and position, such as pneumonia, laryngeal or tracheal catarrh or ulceration, the formation of abscesses, tuberculosis, or other lesions of similar type, may occur, even without further acute attack of respiratory interference, and end fatally possibly years later. Certain animal and vegetable bodies, after being bathed in the warm moisture of the parts, may swell, and thus give rise to more and more serious symptoms of asphyxiation hours after their entrance into the larynx.

For the purpose of the present discussion these various after-effects may be dismissed because of their similarity to the primary effects or because they have little judicial application. So, also, the entrance of such small objects which, on account of their size, are unable to produce a fatal occlusion may be set aside as not germane to the subject.

If, then, in swallowing or breathing, such an accident of occlusion

should occur, the patient is at once seized with distress and apprehension. The demand for breath is almost immediate and quickly becomes violent. If sitting, he rises with a rush, grasps his throat with the hand, stretches out the neck, and gulps to endeavor to dislodge the intruding mass. All sorts of attitudes and contortions are attempted for the same purpose, and the most violent efforts at coughing are exerted involuntarily. The face, at first pale, shows signs of agony, and becomes quickly deeply suffused and cyanosed. The eyes become prominent, the mouth is open, the tongue often extended. Saliva drips from the mouth, and foam, often tinged with blood, appears at the lips. Vomiting may take place, and the involuntary discharge of urine, gas, or feces. The face is bathed with perspiration. In a few moments the victim falls unconscious. The violent play of the respiratory muscles continues for one or two minutes and then ceases, with perhaps one or two gasping efforts subsequently. The pulse, at first quick and full, becomes tumultuous in a few minutes, and then gradually diminishes in force and fulness and becomes weak and irregular, ceasing finally in eight, ten, or more minutes. With it the life of the unfortunate one stops. The dyspnea of partial occlusion is peculiarly slow when the obstructive substance is located at a high level, as in the trachea or larynx, but is characteristically rapid when the obstruction is located in the bronchial tubes, particularly in the smaller ones.

Just as in other forms of respiratory interference, considerable variation may be manifested in individual cases, from the completeness and suddenness of occlusion and from the natural resistive power of the individual. Death sometimes is immediate from syncope, and the countenance remains pale and placid; or if the occlusion is not quite complete and the patient vigorous, the violence of respiratory effort and the degree of facial contortion and cyanosis are extreme.

Postmortem Appearances.—On external inspection there may be an entire absence of any signs suggesting death by asphyxiation. The face may be quite normal in its appearance, both in color and in the composure of the features. Often, however, the face is deeply cyanosed, and when found, the eyes are open, prominent, staring, with widely dilated pupils, and the features may be much distorted. The absence of local impediment to the passage of blood to the trunk, however, permits this appearance with much less frequency than in stragulation. The pulmonary stagnation may, however, be so great, and the distention of the right heart so marked, as to prevent this movement from the head and neck, and there is, therefore, a proportion of cases, somewhat less than half, in which the cyanotic condition of the countenance is pronounced. As a rule, there is also considerable congestion in the upper extremities. Lividity of dependent parts is marked. Rigidity usually comes on early. On examination of the body after section the right heart and larger veins of the trunk are found full of dark, fluid blood, the left side and arterial system being relatively bloodless. The lungs are usually deeply congested, often marked with small subpleural ecchymoses, sometimes emphysematous along the borders. There may

also be found some pericardial ecchymoses. In those patients who die quickly from cardiac inhibition or syncope these appearances in the heart and lungs do not obtain. The heart contains blood, partially clotted, in the cavities of both sides, and the lungs are not especially hyperemic—perhaps they may be actually pale.

On examination of the respiratory passages the mucous membrane throughout is, as a rule, hyperemic, and there is considerable mucous secretion, with perhaps some blood, over its surface. At the level of the foreign body the membrane is usually quite red and swollen, with possible marks of injury due to the intruding substance. The foreign substance itself may be found anywhere from the larynx down to the bronchial tubes of the second or the third division, although in the latter case it is not likely that death was rapid in its onset, and therefore not likely to have much legal interest. Death by choking is usually caused by comparatively large objects, which are rarely found below the larynx. As a rule, such have had little opportunity to undergo substantial change. When the objects have been retained a long time, they may be found more or less disintegrated, even such substances as silver coins undergoing chemical changes into the sulphid, and are thus recovered or expectorated after the lapse of months.

When the foreign body has thus been retained for a time before the fatal paroxysm of asphyxia, the local appearances are even more pronounced. The mucous membrane in the vicinity is thickened, often ulcerated; there may be abscesses in the surrounding tissues, areas of consolidation in the lungs, or tuberculous changes of various types. In acute choking the brain is hyperemic if freshly examined; later it is normal, except in the dependent portions, to which fluids gravitate.

In such an examination there is nothing characteristic of the particular mode of death save the discovery, *in situ*, of the cause of the occlusion; the general features are common to other forms of asphyxia.

Treatment.—Prompt action is necessary. The patient should be pounded vigorously on the back in order to dislodge the offending material either mechanically or by exciting particularly strong respiratory efforts. The head and shoulders should be lowered face downward, or the body even inverted to aid by gravity the expulsion of the mass. With the hand properly guarded by a handkerchief, the finger should be inserted into the mouth, and it may sometimes succeed in removing the substance if it is in the pharynx or above the edge of the glottis. Should such efforts succeed early, the patient usually takes a long, full inspiration, and the impending trouble quickly disappears, leaving the patient prostrated and weak for a time. If they are insufficient, and if instruments for the observation of the exact position of the obstruction and for its withdrawal are at hand, they should be employed at once; if not, tracheotomy below the supposed level of the mass should be performed immediately. When the patient has ceased breathing, artificial respiration should be performed, a means of entrance of air having been provided, and the usual treatment for asphyxiation practised.

Legal Considerations.—Aside from choking during the course of a natural disease, this mode of death is almost invariably accidental. As a means of suicide it is rarely resorted to save in desperation, and it is hence most common among the insane of asylums and in prisons. As a means of homicide it is rarer still, being practically impossible unless the victim is already unconscious and helpless from prior violence, sleep, anesthesia, or similar states.

Careful examination for the existence of signs of such violence and inquiry into the collateral evidence as to the state of consciousness at the time of occlusion may give important results, although rarely are they positive. The mere discovery of an occluding mass in the respiratory path cannot be held to have proved death by such occlusion. Such a mass may have been inserted, at least into the fauces, after death, to divert suspicion, as has been recorded in a few instances. It is necessary, therefore, that the physician establish as fully as possible the absence of other lesion to account for death, and the existence of general signs compatible with death by asphyxiation in this manner before it is possible to render a verdict of death by choking. It is to be remembered that sometimes, even if the foreign body is too small for complete occlusion at the level of its lodgment, it may induce, by irritation, a reflex spasm of the vocal cords or of the muscular fibers in the margin of the glottis, thus leading to complete closure, at least for a length of time sufficient to precipitate death; and that the mere presence of such irritation may reflexly cause syncope, irrespective of the size and character of the irritant substance.

(b) **Death by Submersion.**—Death by submersion or drowning is the fatal result of asphyxiation induced by complete or partial submersion of the subject in water or other liquid medium. Such a definition, however, must be subject to various exceptions and additions. While, as a rule, in drowning the body of the victim is completely surrounded by liquid, cases of death from partial submersion are not infrequent. Some years ago an epileptic patient of one of the writers, while walking upon a low sandy beach, fell in a paroxysm with face down, causing by his spasmodic movements a small excavation of $1\frac{1}{2}$ inches in depth in the sand beneath his face. This small depression quickly filled with water, and he was found dead from asphyxiation in this position about an hour or more after the occurrence.

Of course, in case of asphyxia from such partial submersion, the respiratory openings must be included in the part submerged. This latter rule does not of necessity prevail in cases where death takes place from syncope, individuals from time to time being known to succumb suddenly upon submersion of the body, but with the respiratory openings not submerged. Such cases are, however, rarely confused with real drowning. Moreover, one is tempted to say of those dying in natural surroundings from edema of the lungs that they drown in their own juices—totally apart from immersion or submersion.

As to the precise mode of death in drowning, asphyxiation occurs in over 90 per cent., failure of circulation from syncope being responsible

as the immediate cause of death in perhaps not above 1 or 2 per cent., while combinations of respiratory and circulatory failure or the mediate influences of apoplexy are likewise extremely low. Mackenzie, of Calcutta, from an analysis of over 300 cases of drowning which were examined by him as police surgeon, has placed death by asphyxia as taking place in over 97 per cent., syncope in but $\frac{1}{3}$ of 1 per cent., and asphyxia and apoplexy combined in the same proportion. About 2 per cent. of the cases examined remained undetermined on account of post-mortem changes. It is probable that these proportions would show a slightly increased proportion of cases of syncope in colder climates, from the greater shock to the nervous system of the unfortunate in coming in sudden contact with the cold water.

Drowning was at one time a legal method of execution, being usually employed in case of women and minor criminals condemned to death. The method prevailed in England until the early part of the seventeenth century, and was in vogue in a few of the continental countries of Europe until the middle of the following century. It is rarely a measure of homicide except in infanticide. It is a frequent method of suicide. Analysis of large numbers of instances of self-destruction show its employment in nearly one-third of such cases. In by far the greatest proportion, however, it is the result of accident. Among individuals, of course, danger of drowning upon immersion is extremely variable from the ability or inability to swim; but such ability is by no means a guarantee of escape from such consequences, since excellent swimmers are often unable to sustain the fatigue of long immersion, and not infrequently succumb suddenly in the water from inability arising from muscular cramps or from syncopal attacks.

Individuals who possess various respiratory defects, such as stammering or asthma, and those who have structural or serious functional disturbance of the circulatory apparatus or its nervous mechanism, are more liable to drowning upon immersion than are normal individuals. In general, vigor, health, and calmness of mind, other things being equal, decidedly diminish the danger in case of impending drowning. Instances of drowning occur more frequently among males than females, but merely because of their more frequent exposure to its conditions. Coldness of the water seems to increase the danger.

Symptoms.—Observation of the subject would indicate that several groups of cases may be separated. In the first place, there are a few cases in which, when submersion has taken place, especially if it has been sudden and the water of low temperature, death is found to have taken place even when the individual is immediately rescued. In most of such cases syncope is the immediate cause of death. It is induced probably by the severity of the nervous shock or by individual inefficiency of circulatory power. A relatively large proportion of this group of cases, however, may be resuscitated if the attempt is promptly and vigorously made, owing to the relatively moderate alterations which have in so brief a period of time been effected. It is probable, as stated by Brouardel, that in some of these cases death occurs from a nervous

inhibition of both heart and lungs, induced by the stimulating effect of the sudden cold upon the recurrent laryngeal, trigeminal, and other nerves known to possess such inhibitory reflexes.

In the much larger group of cases in which asphyxiation is the direct mode of death there exist at least two possible methods of its production. Thus in one group the asphyxia is primarily due to a spasmodic closure of the glottis from the direct irritation of the water entering through the mouth and nose, and about to penetrate the respiratory passages, or from nervous reflex to the sudden chilling of the external surface of the throat. It has been shown experimentally that laryngeal spasm may be induced by mechanical irritation of the skin over the larynx and anteromedian portion of the neck. In this group the victim, falling into the water, usually sinks at once and remains below the surface. As in the other cases of asphyxia, unconsciousness ensues in the course of some seconds; after a few futile convulsive efforts to breathe the respiratory attempts cease, and after some minutes the heart stops. Here, after a minute or two, the spasm of the glottis relaxes, while there are but few and feeble inspiratory efforts and but little water gains entrance into the respiratory tubes, unless submersion is prolonged, when further small amounts may gradually enter as a post-mortem phenomenon.

In by far the greatest number of cases, however, little or no actual spasm of the glottis takes place; and asphyxiation occurs from the actual entrance of water into the larynx, trachea, bronchi, and even the terminal saccules of the lungs, or there may be a combination of both these factors of respiratory obstruction. The individual having been submerged struggles to regain the surface to breathe. As soon as the surface is reached he attempts, by a long inspiration, to regain his breath; but is likely to draw a small amount of water into the larynx with the air. Owing to the irritation thus caused, violent expulsive efforts, partly involuntary, are made with sputtering and coughing. The real effect is rather to diminish the air in the lungs, accelerate pulmonary congestion, and non-aëration of the blood, and incidentally to increase the relative weight of this portion of the body and favor further sinking. Considerable water is likely to enter the respiratory paths in such instances, penetrating at once to the air-vesicles and passing by osmotic action into the blood. In such cases more or less water is swallowed, and partly from spasmodic action of the diaphragm the contents of the stomach thus dilated are likely to be regurgitated, and may be drawn into the respiratory tract from the pharynx. The struggle for life is violent; the individual grasps at even the slightest means of support, and often in the blindness of his efforts wounds the fingers and hands in many places. Even when completely submerged and upon the bottom, he wildly and futilely tries to lay hold of surrounding objects, often grasping handfuls of the mud about him and frequently getting the mud and sand of the bottom beneath the finger-nails. Small quantities of the same material are likely to find their way into the stomach and respiratory paths in his

mad efforts to inspire and clear the obstruction to respiration. After the first few moments of respiratory obstruction, which is usually at first incomplete, the face becomes cyanosed, the eyes bulge, the features become contorted, the respiratory movements tumultuous and spasmodic, the pulse rapid and violent. From the violence of his efforts the contents of the bowel and bladder may be voided. After one or two, or at most three or four minutes, in ordinary cases, respiration has ceased; but for a number of minutes (five or six or more) the heart continues to beat, gradually failing in strength, rhythm, and rapidity, and usually stopping in systole. The entire process may be completed in three or four minutes, or may be prolonged to two or more times this period.

It is said by persons who have been rescued from drowning that in the first few seconds or minutes of submersion the mind possesses the activity noted in other forms of asphyxiation. The memories of years flood the mind, and the most vivid realization of the impending death and its consequences rushes to mental view. The head seems full of bursting; a dull general head pain is realized; there is a roaring or ringing sound in the ears. The sensation of want of breath becomes absolutely imperious, and in spite of every realization of its futility, inspiration is attempted and water drawn into the respiratory tract. As the asphyxia becomes more pronounced the mental activity gives place to a feeling of resignation, of peace, of carelessness of results, and in a moment more unconsciousness supervenes. In this form the chance of resuscitation is much less than in either of the former varieties.

Postmortem Appearances.—Considerable variation is possible here, as in other forms of asphyxia. The body usually becomes rigid early, within the first hour, especially when vigorous struggling has taken place. In syncopal cases, however, it may be much postponed. The surface of the skin is often marked by "goose-flesh," which, being the result of contraction of the erector pili muscle-fibers in the skin, is commonly regarded as a vital action and as evidence of the submersion having taken place during life. Immediate submersion of the body after death from other cause may, however, be attended by the same phenomenon, especially if the water is of low temperature. On the other hand, it has been noted that when the drowning has taken place in comparatively warm water, as in tropical climates, this appearance is often wanting. The general surface of the body is, as a rule, pale. This is to be expected, from the action of the cold upon the general surface, and the distention of the larger internal venous channels. There may be small patches of reddish discoloration in variable situations, such as occur with other exposure to cold, but they are unusual and of slight degree. The face, however, in most cases when examined early after death, if death has actually been by asphyxiation, is livid; while in all cases of syncopal death and in a small proportion of those dead from asphyxiation (where time, position, and gravity of the blood and only slight degree of congestion favored drainage) the face is likely to be pale. This congested condition of the face is not to be mistaken for the

discoloration of putrefaction, which in cases of drowning generally is first manifested about the face and neck; this latter discoloration is usually of a deeper and more violet or green hue, and is generally attended by a greater swelling of the tissues. When the drowning has occurred in water of low temperature, and especially when death has come on rapidly and without much struggling, the face is, as a rule, pale. This is owing to the fact that drainage of the superficial tissues about the head is favored by the constricting influence of the cold water directly in contact, and because the body is not, as a rule, at once recovered. In the majority of cases the face is placid. The eyes are generally only partially closed, and the pupils dilated.

Not infrequently, as observed in a large proportion of several hundred bodies among those dead in the great flood at Johnstown in 1889, in those cases in which asphyxiation was gradual and accompanied by severe exertions, conjunctival ecchymoses varying in degree may be found. These exist entirely apart from direct violence. The testimony of persons resuscitated or rescued before unconsciousness had ensued, who may bear the same peculiar sign, is conclusive on this point. The ecchymoses are the results of the intense congestion. At times such suffusion may cover the entire exposed part of the sclerotic and even extend into the tissues of the eyelid on the dermal surface. Such marks should be recognized as not necessarily the result of external violence. The mouths of those dead from drowning are commonly partly open and the tongues in normal position, occasionally between the teeth. The joints are usually somewhat flexed, either from the contraction of rigidity being more powerful in the flexors on account of their greater bulk than that of the extensors, or rigid in a position of flexion assumed just before death. Thus often the hands are found tightly grasping various objects with which they come in contact in the struggle of the victim; and it is known that, at times, owing to a tight grip of grasses, roots, or other matters upon the bottom, the individual has been held beneath the water and the rapidly appearing rigidity of death served to maintain the grasp and keep the body in position until relaxation from putrefaction has set the corpse free.

In examining the hands note should be made of the character of substances thus held and of the mud or sand found beneath the nails, for comparison with the bottom upon which the person met his death. So, too, the hands and fingers should be observed for excoriations, which are likely to be produced during the violent struggling. It should be remembered that after a few days there is usually in any case some dirty, slimy deposit beneath the nails and in other protected parts of the body, and this bears no relation with the material scraped up during the death agony. When submersion has extended several days or longer, the palms of the hands and soles of the feet are generally very white and shriveled, and the epiderm may be loose from the corium beneath. The genitalia are usually found more or less contracted and small; but if the body is recovered early and the medium is not cold, the reverse may sometimes be encountered and the penis be found semi-erect.

On postmortem section the blood often oozes freely from the slightest cut, especially when death has been recent. The heart is found, as in other forms of asphyxia, with the right side well distended, and the left small and empty. The blood is almost always found in the venous system, dark and fluid. Clots are less rare than in the ordinary forms of asphyxiation, but are rarely marked or large. In those cases dying of syncope the left side of the heart may contain blood, and clots may exist in both cavities. As a rule, there is a slight excess of fluid in the pericardial sac and likewise there may be found a small quantity in the pleural cavities. The lungs are almost invariably large, rather firm, boggy, and crepitant. They are usually uniformly hyperemic, the dependent parts of a deeper hue than the superior parts; and in many instances the latter surfaces before section have a dirty grayish hue from a relative absence of blood in this portion. On section, however, the blood drips from them freely.

On examining the respiratory passages various appearances may be found. In some cases, especially in those dying rapidly or immediately after submersion, nothing, or at most slight hyperemia of the mucous membrane may be noted. But in the cases dead from even moderately gradual asphyxia there is to be found a variable amount of water in the respiratory tubes. This amount is, as a rule, not great—a few drams or ounces—and is seen mostly in the trachea and larger bronchial tubes; but it is probable that this in nowise represents the real amount of such fluid which may have entered the larynx. The condition of the lungs; the degenerated and desquamated alveolar epithelium; the hydremic state of the blood upon minute examination; the fact that the fine grit and mud of roiled water are to be found even in the smallest ramifications of the air-passages—the fact that in experimental drowning of animals in colored waters these colors have been found in the respiratory terminal areas—all point to the fact that in such condition a rapid osmotic process takes place with the absorption of a very material portion of the water into the blood.

Often no water at all can be detected, but there is usually a quantity of a fine, white, lather-like froth all through the bronchial system and in the trachea and larynx. This is supposed to be due to the violent mingling of the respiratory air with the water entering the tract, and is hence regarded as a sign that death took place by a slow asphyxiation from submersion. It forms more freely in the smaller tubes, where the size of the passage compels the mixture of air to be the more thorough, and is similar to the fine froth sometimes seen in these passages in death by pulmonary edema. Its existence in notable amount in the larger passages is, therefore, significant of the large degree of obstruction by fluid, and indicates that at the time of asphyxiation these passages were largely occupied by fluid. This froth is much finer than the mucous blebs often encountered along the respiratory mucous membranes. It is white in color, and may persist for ten or twelve days after drowning if the body remains submerged. In addition to this froth it is quite common to find the mucous membrane more or less

reddened. In some instances the epiglottis is found standing almost erect and the glottis open; in other instances the former is normally adjusted. In examining the larynx, trachea, and bronchi attention should be directed to the existence of bits of foreign matter, as mud or sand, carried in with the penetrating water.

The subpleural and pericardial hemorrhages noted in other forms of asphyxia, notably in throttling and in any mechanical suffocation in the young, are occasionally seen in cases of drowning, but are infrequent. The fluid in the pericardial and pleural cavities is sometimes tinged with blood.

The abdominal organs are almost uniformly congested and dark in color. The stomach, in a large proportion of cases, notably those dead by a slow, struggling form of asphyxiation, is likely to contain more or less water, swallowed in the course of the process. This is not invariable by any means, and in order to determine this as clearly as possible, careful examination for foreign matter known to exist in the water surrounding the body when drowning, as bits of wood or leaves, mud, and sand, should be made. The diaphragm is often found markedly depressed, probably from the fulness of the thoracic cavity.

In the third variety of drowning, and to a less degree in the second, it is common to find marked venous congestion of the brain substance. Very rarely actual apoplectic areas exist. In those cases where the head has remained more or less elevated after death much of the congestive appearance may have been removed by gravitation of the blood. A sign of considerable importance may sometimes be gained by aspiration of the middle ear, as a small quantity of fluid may be forced into this cavity, especially in the violence and confusion of inspiration and swallowing, with the mouth full of water. It is not known that water can force its own way into this cavity after death; and its presence is hence regarded as important evidence that submersion was ante-mortem.

As the result of putrefaction the signs recorded are subject to more or less modification. The rapidity of appearance of putrefaction depends upon the temperature of the water and depth of submersion, as well as upon individual peculiarities of the tissues of the body submerged and the character of water in which the corpse is submerged—whether fresh or strongly saline, whether stagnant or in constant motion. Of course, the first of these factors is determined largely by the season and climate. In general, it may be said that these signs of decomposition in water require at least twice the time as in air. Putrefaction in these cases, as a rule, is first manifested about the face and neck, then over the chest, groins, thighs, arms, and abdomen, to a great extent a reversal of the usual order of putrefaction in the air. This peculiarity is, however, more apparent than real, and probably depends largely upon the development of considerable quantities of gas of putrefaction in the blood in the larger internal veins. As a result of the pressure thus caused the liquid blood is forced into the capillary areas of the skin and mucous membranes in sufficient quantity to give rise to the deep discoloration

of the early stages of putrefaction. The surface of the face and neck is first discolored because of its vascular capacity, while for a contrary reason the abdominal wall is late in being thus involved. As a further consequence of this phenomenon the parts to which this excess of decomposing fluid tends take early part in the further putrefying changes. The face and neck hence become deeply discolored and bloated, both because of the blood in the tissues and because of the gases of putrefaction which develop and are largely retained in the structures. This swelling of the countenance entirely obliterates the expression and often renders the features unrecognizable.

Owing to the admixture of gases, in their escape from the respiratory passages, with the mucus and fluid therein, a large amount of rather coarse, often reddish-tinged froth is formed, and may frequently emerge from the nostrils and mouth. This should not be mistaken for the fine, white, lather-like froth already described. The latter is likely to have disappeared in the course of putrefaction, and at best is not likely to persist more than ten or twelve days. The development of gases of putrefaction going on to a greater or less extent all over the body causes wide-spread bloating and diminishes the relative weight of the corpse, which in consequence becomes lighter than water and rises to the surface. A popular idea ascribes an influence to loud sounds in thus causing the reappearance of bodies submerged, as the detonation of cannon or the roll of thunder. The real cause for the unquestioned relationship is, however, not in the sound itself, but in the mechanical jar or tremor, which may be sufficient to dislodge the body from slight hindrances to its ascent to the surface. The greater specific gravity of the salt water, together with the influence of the motion of tides, and, to a certain extent, of the waves, induces an earlier reappearance of the bodies of those drowned in the sea than when submerged in quiet fresh water. There are some collections of water, such as Lake Superior, from which it is said submerged bodies do not reappear at all. These instances are probably to be explained upon the supposition that deep currents sweep the corpse away from the locality where death took place, and for this reason it is not discovered before complete decomposition. It may be said, in general, that the bodies of those drowned always rise to the surface somewhere and at some time; but that, owing to the influences of currents and storms, the place of reappearance is not always close to the spot where drowning occurred; and that inasmuch as all circumstances influencing putrefaction must likewise influence the phenomenon of ascent to the surface, a great variability as to the time must be accepted.

The season, climate, depth, motion, and specific gravity of the water, as well as certain peculiarities of the body, such as the amount of adipose deposit, all must be considered in estimation of the probable time in any given case. In cold climates, especially in winter, drowned bodies do not, as a rule, emerge to the surface of the water until the following spring; on the contrary, in warm climates, in summer, bodies may rise on the second or third day—exceptionally upon the first.

Examination of the surface of such bodies will show that when putrefaction is well advanced, and probably dependent upon the relaxation and swelling of the tissues due to this process, the *cutis anserina*, or "goose-flesh," so frequent an appearance in recent cases, is wanting. Excoriations and chafings of the skin by friction of the surface of the body upon rocks or other hard substances are likely to be encountered in cases where submersion has been prolonged; these marks become dry, hard, brown, and parchment-like a short time after exposure to the air. Beneath the hand, both on light and firm pressure, a fine crepitation due to the gases infiltrating the subcutaneous and muscular tissues can usually be made out. Here and there, especially in the palms and soles, the epidermis is readily detachable in sheets.

On internal examination the evidences of putrefaction are quite apparent. The heart and larger vessels are not so full of blood as in recent cases. The endocardium, inner coat of the blood-vessels, and the mucous membranes of both the respiratory and alimentary canals may be stained red by the hemoglobin of the decomposing blood. Bubbles of gas can often be demonstrated in the smaller vessels, and the intestinal canal is highly distended with gas. The staining referred to is not limited to the parts mentioned, but is likely to extend more or less diffusely throughout highly vascular parts. In the intestines the entire wall is often so deeply reddened as to suggest an active inflammatory process; it is, however, readily distinguished from such, and may be definitely told by examination under the microscope without the use of staining reagents, as the yellowish-red tint of the body of cellular elements and the unstained appearance of the nucleus will quickly gain the attention.

Recently Alexander Gettler advocated the determination of the chlorid contents in the right and left heart chambers as a reliable test for drowning. This test depends upon the entrance of water into the lungs during drowning, which, by osmosis, dilutes the chlorid contents of the blood. Normally the chlorid contents in the blood of the right and left chambers is about the same, the greatest differences being 5 mg. in 100 c.c. of blood. In all cases of drowning examined by Gettler the difference was always greater than 5 mg., ranging from 19 to 294 mg. When drowning had taken place in fresh water the left heart chamber always showed the lower chlorid contents; the opposite occurred when drowning had taken place in salt water. The degree of difference depends upon the amount of water going into the lungs, and on the time interval between the entrance of water and death. It must be remembered that no water can get into the left heart if the individual is thrown into the water after death.

Gettler's test seems to be a very simple but exact method, and should be tried in all suspicious cases. The chemical procedures are sufficiently simple to permit its routine use.¹

¹ For details the reader is referred to Gettler's paper in Jour. Amer. Med. Assoc., 1921, 77, 1650.

Treatment.—Attempts to resuscitate those apparently dead from drowning are more successful in instances of those becoming immediately unconscious when falling into the water, and in those in whom death has apparently taken place with little struggle, and asphyxia has occurred mostly from spasm of the glottis—in other words, in all those cases in which little water has penetrated the respiratory passages. Instances of success have been recorded after such patients have been submerged twenty or thirty minutes, but where submersion has lasted for more than four or five minutes, there is usually little hope of success; and where asphyxiation has been general and much water has entered the respiratory passages in the wild struggle for life, attempts to revive almost always fail.

As soon as the body is recovered it should be placed in position, with head and shoulders depressed and face downward, to favor drainage of fluid from the mouth and respiratory tract. If this is unsuccessful, or as soon as drainage, which is aided by moderate motion of the body and pressure on the chest, is accomplished, artificial respiration should be instituted and persisted in for hours if necessary. Forcible traction of the tongue after the manner of Laborde, about eighteen or twenty times a minute, synchronous with the inspiratory movement of the artificial respiration, may be of distinct aid in stimulating the respiratory act. So, also, electric stimulation of the phrenic nerves may be of service. In addition to such efforts hypodermic administration of cardiac stimulants, venesection, the external employment of friction and heat to aid in re-establishing circulation should be practised as required.

An excellent method of re-establishing respiration is that of Professor Schäfer. He describes the method as follows: Lay the subject face downward on the ground, then without stopping to remove the clothing the operator should at once place himself in position astride or at one side of the subject, facing his head, and kneeling upon one or both knees. He then places his hands flat over the lower part of the back (on the lowest ribs), one on each side, and then gradually throws the weight of his body forward on to them so as to produce firm pressure—which must not be violent or upon the patient's chest. By this means the air, and water if any, are driven out of the patient's lungs. Immediately thereafter the operator raises his body slowly so as to remove the pressure, but the hands are left in position. This forward and backward movement is repeated every four or five seconds; in other words, the body of the operator is swayed slowly forward and backward upon the arms from twelve to fifteen times a minute. This should be continued for at least half an hour, or until the natural respirations are resumed. While one person is carrying out artificial respiration in this way, others may, if there be opportunity, busy themselves with applying hot flannels to the body and limbs, hot bottles to the feet, but no attempt should be made to remove the wet clothing or to give any restoratives by the mouth until natural breathing has recommenced.

The use of the mechanical pulmotor, when quickly available, in the hands of one experienced in its application is to be advocated here and whenever artificial respiration is required; but time should not be lost in sending to make such apparatus available, and its use by those not familiar with it, in the opinion of the writers, may easily become an abuse and productive of harm to the pulmonary structures.

A curious amnesia often follows resuscitation, the entire circumstance of drowning and associated events often being a complete blank to the patient. Constant attention should be given the patient for a day or more after resuscitation, lest sudden syncope set in and unexpectedly terminate the patient's life.

Legal Considerations.—For the legal physician there are three questions of particular interest in this connection: Was death actually due to submersion, or was the body placed in the water after death from other cause? Was submersion accidental, suicidal, or homicidal? How long has the body been in the water?

In the determination of the first of these questions it should be acknowledged in the beginning that there is no one absolute sign of death by submersion. The best evidence is obtained by the combination of all the phenomena already detailed. Of the individual appearances, probably the most characteristic, when present, is the lathery foam found in the larynx, trachea, and bronchial tubes. It is, however, not likely to remain beyond ten or twelve days after submersion when the body is in the water, and after the body has been removed from the water may disappear in a few hours. It disappears quickly, also, after putrefaction has set in, the coarser, tinged froth of this stage entirely obliterating it. In the performance of the autopsy for the purpose of observation of this feature and others in the same situation the parts should be so opened as to be examined *in situ*.

Perhaps the next most valuable index is the discovery of the presence of water in the respiratory tract and in the stomach, and the recognition of its identity, from contained particles of peculiar character, with that in which submersion took place. The amount of water actually found in the lungs and trachea is rarely large—usually not more than a few drams, rarely more than an ounce or two. This, however, should not be taken as an indication of the amount which actually entered the larynx, since a considerable part is diffused into the blood throughout the lungs, thus contributing to the edema and to the size of these organs. Careful search for particles of extraneous matter, such as sand-grains, mud, or vegetable matter which may have been carried in with the water, should be made for the purpose of identification with similar matter held in suspension in the water in which such body has apparently been drowned. As to the water in the stomach, little importance can be attached to small quantities, since it may have been swallowed naturally shortly before death. If, however, more than half a pint is found, or when mud, sand, and bits of sticks or grasses are also found, it may be presumed to have entered during the death struggle. It is not probable, as shown by the experi-

ments of Tagerlund and others, that water can enter into these situations after death except under considerable pressure; and the importance of the sign in question may therefore be highly regarded. Similarly, when present, the existence of water in the middle ear is of great value in indicating this mode of death.

Much importance has been placed upon the presence of *cutis anserina* by some writers. This may often be found in death from other causes, as sometimes in death by freezing. It is, moreover, frequently absent in instances where death from submersion took place in water of moderately high temperature, and regularly disappears after putrefaction is well established. While the large size, edema, and emphysema of the lungs constitute a valuable confirmatory sign, this state is unquestionably influenced largely by putrefaction, and might be closely simulated by putrefactive changes in the lungs of those submerged after death.

The fluid state and hydremic condition of the blood possess similar importance; the blood, however, may present similar gross appearances in other forms of asphyxiation and intoxication, and is not always fluid, some clots frequently being found, especially in those dead from syncope, when likewise little or no hydremia prevails. The value of Gettler's test determining a notable difference in chlorid content of the blood in the right and left cardiac chambers is important (see page 385). The order of putrefaction is highly suggestive, but here again absolute certainty fails. A similar order may occur in cases where the blood has remained fluid after death, as in other forms of asphyxia.

The value of external marks, as of injury, is much diminished from the fact that such marks might be produced after death by drowning, by fish- or crab-bites, by chafing or beating of the body against rocks, or may have existed prior to the time of death and have had no influence in its production. A careful consideration of such marks, as to their position, character, and extent; the existence of tumefaction or other signs of inflammation about them; of their relation with deep-seated injuries; with the general postmortem findings and with any possible external circumstances or testimony, will usually lead without much difficulty to their true significance.

In general, then, it may be said that, with the modifications and special features already indicated, death by drowning may be predicated with a reasonable degree of certainty by a combination of these signs upon the body found in a fluid medium—face and surface pallid or discolored, especially about the head and neck, perhaps in the latter case much swollen; froth of a peculiar character, water and foreign particles in the respiratory tract; water in the middle ear and stomach; lungs edematous and emphysematous; diffuse and marked congestion of lungs, abdominal viscera, and brain; blood dark and fluid, and present mostly in the right side of the heart and in the venous channels, and more or less postmortem staining by hematogenous pigment of the tissues, especially the endocardium, lining of blood-vessels, and mucous membranes of the respiratory and alimentary tracts.

In endeavoring to determine whether the drowning was accidental, suicidal, or homicidal, the main reliance must be placed upon collateral evidence. Except in cases of children and those known to have been similarly helpless against force it is reasonable to regard the case as either accidental or suicidal, rather than homicidal, in the entire absence of signs of external violence from the body found dead from drowning. Homicide is not, however, entirely eliminated, since it is possible that even the most able-bodied might at times be thrown by an unexpected push into the water without the least sign of such violence having been produced upon the body. On the other hand, when distinct signs of violence, such as severe bruises, cuts, shot-wounds, fractures of the skull, imprisonment in sacks or by bonds, are found, the first thought naturally refers the death to an author other than the dead. Yet it is a frequent thing for suicides to double their efforts at self-destruction—to shoot themselves while in such position that when falling they must be precipitated into the water and thus insure the fatal result; to wound themselves by cut or stab and then throw themselves into the water with the same intent; even to fasten weights about the neck or elsewhere to make submersion doubly certain. In falling into the water accidentally or as a result of suicidal impulse the body might, moreover, sustain more or less severe injuries, as from striking upon a pier, a rock, a log, or the bottom. Sharp contact with the surface of the water is capable of producing splits of the skin and underlying tissues which may closely resemble cuts by some dull instrument, fractures, and contusions. In all such instances, therefore, aside from other testimony, signs of injury upon the body or of disability must be considered in the light of possible self-production or of accident before suspicions of homicide are definitely entertained. In all cases of drowning, moreover, the history of pre-existing disability of any sort, of epilepsy or insanity, as favoring accidental submersion or suicide, must be given due weight.

Homicide by drowning, save in case of infanticide, is rare, and is rarely free from signs of the violence necessarily employed. Suicidal drowning is, however, very common, upward of one-third of all suicides being accomplished by this means. In cases of suspected infanticide by drowning care should be exercised to determine whether the infant had been born alive or whether a still-born infant had been thrown into the water for purposes of concealment or economy. The usual hydrostatic test to determine distention of the lungs may be employed to answer this question. Evidence of strangling or suffocation or of other means of destruction should likewise be sought for, drowning being affirmed only in the absence of these and in the presence of the usual signs of submersion.

For the purpose of concealment of crime it is not an infrequent practice to throw murdered bodies into the water. Serious hindrance to justice may thus sometimes be accomplished, since it is impossible to declare unreservedly that death by submersion may not have occurred in absence of the signs just detailed, which are usually present, and

because putrefaction may in great measure obscure or destroy the signs of violence employed. In cases where suspicion of such practice has arisen it should be remembered that the group of signs of submersion cannot be simulated by immersion after death, except—and then not completely—in case of death by some other mode of asphyxiation; and when such signs are fully established, previous violence was not directly the cause of death, but could have been only contributory. In cases where such signs of death by drowning are absent, while it is possible that drowning did take place, it is impossible to make affirmation upon this point, and the importance of the evidences of violence, together with the collateral testimony, must govern the decision. As a general rule, cuts and similar wounds produced before death and submersion will retain evidences of blood coagula; while similar lesions occurring after submersion, even though before the actual time of death, will, from the action of the water on the escaping blood, be free from such coagula. Therefore, in the determination of the significance of wounds and abrasions in bodies found submerged, due attention to the condition of the surface of the wound may establish the fact of production before submersion or during submersion, a decision, when possible, often of extreme value judicially. Any scab or suppuration or granulation on the surface of the wound certainly indicates its existence a number of hours or days before death. The value of all these evidences is, however, impaired by the fact that they can be detected certainly only in comparatively fresh bodies.

In the determination of these points, as well as in the establishment of identity in individual cases, and for other obvious reasons, it is often necessary to estimate the probable duration of submersion. It is necessarily impossible to give any exact opinion upon this question, since so many factors exist capable of modifying the basis of judgment. Whatever opinion, however, is given, such must depend upon the alterations in the body from maceration and putrefaction, where previous knowledge of the case is not had. An approximate idea may be had from the following statements, originating with Devergie, and based upon observations made during the severe winter of 1828–29 in France. During the first three days little or no change can be noted from the state of the body immediately after death. Cadaveric rigidity is usually pronounced. On the third or fourth day the epidermis of the hands begins to blanch, especially over the thenar and hypothenar eminences. From the fourth to the eighth day the remainder of the palm becomes white, and cadaveric rigidity disappears. From the eighth to the twelfth day the dorsal side of the hands and the plantar surface of the feet become blanched; the face becomes flabby and slightly discolored if previously pallid. By the fifteenth day the palmar epiderm has begun to shrivel and to show peculiar corrugations; the face has become slightly swollen and dark in patches; the subcutaneous tissue over the chest is red, and some greenish discoloration is likely to be present about the upper part of the sternum. At the end of the first month the epiderm of the palms and soles is very white and shrunken, just as if from pro-

longed poulticing; the face is dark and red, the lips and eyelids are greenish, the hair and nails are adherent, and the lungs are emphysematous. At the end of the second month the epiderm of the hands and feet is likely to be more or less detached from the true skin, the nails adhering to the epiderm, the whole somewhat resembling a glove. The face is dark and much swollen, and the lips are swollen and apart; the discoloration from putrefaction extends to the shoulders, upper part of the abdomen, sides, and about the perineum. The heart is generally nearly free from blood, the endocardium of the side which contained blood at the time of death is stained, as are the mucous membranes of the respiratory tract and alimentary canal; the hollow organs and vessels generally are distended with gas. By the end of two and a half months the epiderm and nails of the hands are completely detached; the epiderm of the feet likewise, but the nails are still adherent; the putrefactive discoloration has extended into the limbs. By the end of another month portions of the scalp, the eyelids, nose, and lips may be partially destroyed, and the nails are entirely detached. After perhaps another month the scalp is entirely destroyed and the skull-cap denuded; saponification may be present if circumstances favor.

After this period estimation of the duration of the submersion is practically impossible. According to the same author, quoted by Briand and Chaudé, from whose work these statements are taken, the difference of seasons may be estimated as follows in the judgment of their effects upon the submerged body:

In summer five to eight hours' submersion corresponds to three to five days in winter.
In summer twenty-four hours' submersion corresponds to four to eight days in winter.

In summer four days' submersion corresponds to fifteen days in winter.

In summer ten to twelve days' submersion corresponds to four to six weeks in winter.

The observations as to the persistence of the peculiar froth in the respiratory tract (lasting ten to twelve days in continued submersion), and of the *cutis anserina*, disappearing in from three to four weeks in water, may be of assistance in the formulation of an opinion as to this matter. However, it must be kept in mind that such statements as these of Devergie are open to great variation, not only the season and climate and consequent temperature of the water, but the depth of submersion, the character of the water, the motion of the water, and the constitution of the body submerged, as well as the state of health, etc., at time of submersion, all entering as factors in the progress of these changes.

(c) **Death from Choking by Gaseous Matter.**—The choking influences of gases manifest themselves in two ways—either by directly provoking a spasm of the glottis from irritation, or by mere exclusion of oxygen from the respiratory tract. The most common of gases acting in such deleterious fashion is carbon dioxid (carbonic acid) gas, marsh-gas, nitrogen, and hydrogen, by excluding oxygen, and such irritant gases as chlorin, ammonia, bromin, or the vapors of the mineral acids, and the irritant poisons such as those used in late war, by causing

spasm of the glottis, may induce asphyxiation; but many which act thus primarily should be classed as toxicants in their further effects.

(1) **Carbonic Acid Gas (CO_2).**¹—This gas, also known as carbonic oxid, carbon dioxid, and “choke-damp,” is the result of complete oxidation of carbon. It arises from gradual organic decomposition, especially of vegetable matter, from fermentations, from the exhalations of animals, and from combustion of all ordinary inflammable substances, as well as from chemical decomposition of the carbonates.

It is a colorless gas, with higher specific gravity than that of air, and therefore has a tendency to collect in depressed localities in unusual proportions. Old wells, mines, pits, caves, and similar situations undisturbed by the diffusing influences of air-currents, are particularly likely to become occupied by this gas, which in such cases is very apt to have been formed within the earth and brought thither perhaps along some water course or merely through the pores of the soil. It is a constituent of some of the natural gases arising from the ground in connection with oil, and often is present with other gases in great quantities in unrefined oil. It is found in the bottoms of fermentation vats which have been nearly emptied, and often accumulates in the cellars where beer, wine, or acetic fermentation is going on in large degree; it may escape in dangerous quantities during the manufacture of aerated waters; it sometimes develops in dangerous amounts in the holds of vessels carrying some fermentable cargo. It accumulates in badly ventilated rooms in which large numbers of human beings or animals are crowded, or in which large numbers of lamps or gas-lights are burned. It is estimated that a single gas-light of ordinary size gives rise to five or six times the amount of carbon dioxid exhaled by one human being in the same time. Another source of importance is in the household fire; and if imperfect draught is provided and poor ventilation of rooms obtains, this gas, as well as carbon monoxid (CO), may accumulate within a short time in sufficient amount to be positively dangerous. In case of conflagrations this gas as well as carbon monoxid, the vapor of water, and other gaseous substances are produced, and together may collect in portions of the building in which no flames exist, and lead to more or less complete asphyxiation of persons entering these apartments. It forms one of the component parts of smoke, and plays a part in the asphyxiation by smoke, which occurs so often in connection with large fires. This gas normally exists in the atmosphere in the proportion of 3 to 8 parts by volume to 10,000 of air. It is capable of producing deleterious results upon prolonged inhalation when present in $\frac{1}{2}$ of 1 per cent. by volume; and when it has accumulated in the proportion of 1 per cent. by volume it is immediately dangerous. In its concentrated form it has a faint sweet odor and taste, produces a decided sense of irritation on inhalation, and a feeling of constriction of the muscles of the throat acting as directly provocative of spasm of the walls of the glottis. The voice becomes high-pitched, even whispering is induced, because of the spasm of the vocal cords, and after one or two inhalations the

¹ Consult also the chapter on Gaseous Poisons, p. 292.

appearances of asphyxia are produced. The face is cyanosed, the eyes are prominent, the mouth is open, and the respiratory muscles are strained; the patient clutches at his neck as if to loosen the spasm; the pulse is quick and bounding. If relief is not given, the individual falls unconscious in about a minute or even less time, and the usual features of death from asphyxia ensue. To bring about such results it is not necessary that the gas should be pure; mixtures of 1 per cent. or more with air are capable of inducing much the same result. When present in the air in smaller amount it is more gradually productive of its results, but acts rather by mechanically taking up the space in the respiratory passages which should be free to proper air. There is a feeling of constriction about the chest, a fulness and pain in the head, a sense of weakness and malaise, usually profuse perspiration, the pulse at first full and quick, but later becoming rapidly weak, the respiration at first shallow, later stertorous and slow, sometimes nausea and vomiting, giddiness, tinnitus aurium, somnolence, and the gradual oncome of unconsciousness. Death commonly takes place in coma. The face in this latter form is usually pale, but may occasionally be deeply cyanosed. At times before the onset of unconsciousness there is a period in which hallucinations and even active insanity are manifested. Death from inhalation of air containing large proportions of this gas properly belong in the group of asphyxia by choking, the group of symptoms and the postmortem signs corresponding closely with other forms of asphyxiation; but in the second or gradual form of death attributed to this agent it is rare that other influences do not combine in such measure as to modify the symptomatology, mode of death, and, to a certain extent, the postmortem findings. Thus in case of suffocation by smoke in connection with conflagrations the part played by the seriously poisonous gas, carbon monoxid, may be more important than that by carbon dioxid.

In situations where the air of some confined space becomes contaminated to a serious degree by the carbon dioxid from the exhalations of the crowded occupants, as in the "black hole of Calcutta" in 1756, narrated by Percy, it cannot be doubted that other exhalation products, some directly toxic, must take active part in producing the dangerous and lethal effects. In those instances of gradual asphyxiation, moreover, the poisoning is more the result of auto-asphyxiation than of the gas contained in the inspired air, the tension of the gas in the inhaled air being such as to prevent the separation of the carbon dioxid from the blood. Hence the effect of the carbonic acid gas in these instances is one rather of suffocation than of choking, the accumulation of CO_2 in the blood mechanically preventing the proper oxygenation of the hemoglobin and producing also narcotic influences upon the nervous system.

Just as in any form of choking or strangulation, *death in a rapid form* may sometimes occur from syncope rather than from true asphyxiation; and there occur, therefore, variable features in the postmortem appearances. Usually the body is cyanosed, especially the face and neck. The blood is dark and uncoagulated, and present mainly in the venous circulation. The right heart is distended; the left, comparatively

empty. The lungs, abdominal viscera, and brain are usually deeply congested. In syncopal death, however, the face is likely to be pale and composed, and the general surface of the body is white; the blood is more frequently found at least moderately coagulated and present in the left as well as the right side of the heart.

In case of death from entrance of the gas in the deeper respiratory passages the influence upon the appearance of the blood of other gases must constantly be thought of, especially that of CO, which may, perhaps, also have been present in the atmosphere inspired. Generally in these cases, when the carbonic acid gas is fully and widely diffused through the tissues and fluids of the corpse, the body-heat and rigidity are likely to be unusually persistent, and putrefaction does not come on readily. The face is usually livid, but may be pale; the countenance is generally calm.

In the absence of gases having toxic action upon the blood, as CO, CN, H₂S, and others, the blood is almost black, usually fluid, but sometimes thick and partially clotted. For purposes of determination the blood may be submitted to spectroscopic examination, when the peculiar displacement to the right of the absorption bands at D and E should be observed. This compound of CO₂ and hemoglobin is very unstable, and immediate examination of the blood is necessary for its demonstration. If the analysis be delayed for some hours the spectrum will be that of oxyhemoglobin. Or the carbon dioxide may be removed from the carefully collected blood by the air-pump or by displacement in an atmosphere of oxygen, and estimated by collection in a solution of an alkaline hydrate as a carbonate. In the presence of the toxic gases, as of CO or CN, the blood is usually of a bright red color, and spectroscopic or chemical examination may be employed to determine their presence.

In all cases of impending death from carbonic acid gas the first necessity is the plentiful supply of oxygen. For this purpose the patient should be removed at once to the open air; inhalations of pure oxygen may be employed. Artificial respiration should be practised and persisted in when necessary; and hypodermic injections of circulatory stimulants, especially nitroglycerin, as recommended by Hoffman, and strychnin freely administered. Bodily heat should be restored by applying hot-water bottles or hot blankets. The surface of the patient should be subjected to friction to aid in restoration of the circulation; and care must be taken to prevent a secondary syncope for a number of days after resuscitation.

Death by this means is almost invariably the result of accident. The victim may have descended into a well for the purpose of cleaning it; or into an old mine-shaft for investigation; or has perhaps entered a large fermentation vat for similar reasons; and death has come almost as from a blow. Appreciation should follow at once in such cases, and chemical examination of the air of the locality and an endeavor to establish the existence of an excess of the gas in the blood be instituted. It should not be expected, however, that a greater amount of the anhydrid will be met in the blood of such cases than in that of those dying

gradually from inhalation of the gas. On the contrary, there will be less, since the respiratory act is more quickly overcome and there is less chance for the accumulation from vital processes before death.

In such investigations, as well as for precautionary measures, a lighted candle should be exposed to the air supposed to have noxious properties, and if the flame is extinguished or materially diminished, it may be concluded that life cannot be maintained therein. Lime-water or other solution of an alkaline hydrate, if exposed to such an atmosphere, soon becomes turbid or has a scum formed upon the surface from the formation of a carbonate. A bit of moistened blue litmus paper is at first reddened, and later bleached. Quantitative estimations may be readily made by the estimation of the carbonates formed in solutions of alkaline hydrates, or by means of a standard solution of an alkaline hydrate, and correction for the unused alkali by oxalic acid, phenolphthalein being employed as an indicator. It should be remembered that a candle will burn in an atmosphere too fully charged with this gas to permit animal life, from 5 to 10 per cent. of CO_2 being required to extinguish the flame, 1 or 2 per cent. being incompatible with life.

Small animals, as white mice, canary birds, etc., are frequently employed to test the respirability of suspected atmospheres, being introduced in open cages and thus compelled to breathe the air under suspicion.

(2) **War Gases.**—In the late war a number of poisonous gases were used, which, by producing intense irritation and inflammation of the upper respiratory passages and the lungs, lead to asphyxial death. The action of many of these is quite complex, and the consideration of their nature not within the scope of this chapter, but a number of these gases must be considered because their use is extending into civil life. Already certain of the milder gaseous poisons have been employed by the police force of some cities to combat entrenched criminals. Much of the subject-matter has been taken from various official publications issued by the Allied armies and especially from the British Memoranda on gas poisoning; further details may be found in these pamphlets.

For practical purposes the poisons which concern us may be grouped into lung irritants and vesicants. The former cause irritation and damage of the deeper respiratory passages, particularly of the alveoli, with resulting inflammatory exudation and the production of acute pulmonary edema. Death is due to asphyxia. Examples of this group are phosgene, chloropicrin, chlorin, and chlor-methyl-chloroformate. The vesicants cause inflammatory disturbance of the skin and conjunctiva, and intense irritation of the respiratory tract; the best known gas of this class is the so-called mustard gas ("yellow cross" gas), or di-chlor-ethyl-sulphid. It must be emphasized that, apart from the direct damage caused by these gases, secondary effects, often depending on bacterial invasion of the injured tissue, are likely to exist.¹

Lung Irritants.—All of the gases of this group produce essentially

¹ See chapter on Gaseous Poisons, p. 344.

the same type of tissue damage and a fairly characteristic clinical picture. The irritation of the pulmonary alveoli which results from their action is followed by the rapid onset of acute pulmonary edema. This fluid interferes with the normal oxygen exchange in the lung and, therefore, causes a severe asphyxial state, indicated by cyanosis, or by pallor and collapse. The face becomes deeply cyanosed or of leaden hue, the respiratory rate increases, the pulse is rapid; there are restlessness, cough, and frothy, often blood-tinged, expectoration. Naturally the symptoms produced depend chiefly upon the concentration of the irritant.

Phosgene (COCl_2) is the most widely used and most intense irritant of this group. The substance was discovered by J. Davy in 1811. At ordinary temperatures it is a gas possessing a very pungent odor, and having a specific gravity of 3.46. The compound is decomposed by water into hydrochloric acid and carbon dioxide. The substance may be made in several ways: one of the simplest methods is by treating equal volumes of chlorine gas and carbon monoxide in the sunlight.

Inhalation of air containing phosgene causes immediate irritative phenomena of the respiratory tract, smarting and watering of the eyes, difficulty of respiration, coughing, and a sensation of tightness and constriction of the chest. With stronger concentrations these symptoms are proportionately more violent, the breathing becomes spasmodic, the chest seems gripped in a vice, and there is usually burning pain in the chest; the breathing is gasping and interrupted by paroxysms of coughing. As a rule, the cough diminishes in fresh air, but the respirations remain rapid and shallow, and deep breathing causes great discomfort and renewed fits of coughing. In the early stages, nausea, retching, and vomiting are usually prominent features, especially in those heavily gassed. In cases exposed to serious concentrations of the poison, exudation of fluid into the alveoli soon commences, and produces asphyxial symptoms by interfering with the respiratory exchange; the want of oxygen is the prominent feature in very severe cases. There is often an extreme restlessness and a moderate delirium; in others, a condition of semi-coma exists. Headache, pain beneath the sternum and in the epigastrium are generally present. The expectoration is often scanty even if the pulmonary edema is marked, but occasionally copious amounts of thin blood-streaked fluid exude from the mouth. In cases in which pulmonary edema develops to a serious extent two groups of symptoms may be observed. In the first group there is marked venous engorgement, the face, lips, and tongue are dusky, the superficial veins may be distended, the breathing is increased in frequency; expectoration of large amounts of thin, frothy fluid is more apt to occur in this group than in the other. The pulse-rate is usually little over 100 per minute, the volume is full and the tension good. The cases in the second group usually have an ashen pallor, the lips and face are leaden colored; the patients are in a state of collapse, respiration is shallow and rapid; though the lungs are intensely edematous there is often little expectoration. The cough is infrequent,

the pulse is very rapid, weak, and running. The prognosis is worse than in the former group. There are, of course, many intermediate types.

The physical signs of phosgene poisoning are those of marked pulmonary edema, although the signs are often indistinct even in advanced cases. Symptoms may be delayed for a number of hours, and not infrequently the gassed patients have been able to go about for several hours with only slight discomfort, and then become rapidly worse. The ingestion of a heavy meal or muscular efforts often bring on violent symptoms.

Four-fifths of the deaths occur in the first twenty-four hours, very few succumb after the third day. Sometimes a man who at first seemed to be lightly gassed may toward the end of the first day become gravely ill, and die; but from the end of the second day onward there is no danger to be apprehended with the less grave cases. Bronchopneumonia not infrequently develops, and is responsible for the occasional deaths that occur later than the end of the first week. As a rule, the patient recovers readily after the third day, but though he may soon be out of immediate danger, complete recovery of cases of even moderate severity may take a considerable time.

The essential postmortem lesions are pulmonary edema, rupture of air-vesicles, concentration of the blood and thrombosis. When death occurs in the late part of the first day the trachea is moderately congested, and this congestion becomes more marked in the smaller bronchial branches. Occasionally there is remarkably little inflammation of the upper respiratory tract. The lungs are usually large, heavy, boggy, edematous, and dusky red. Patches of emphysema alternate with areas of collapse. The cut-section drips frothy blood. Sometimes interstitial emphysema extending to the mediastinum is found. The pleural cavities usually contain varying quantities of clear or blood-stained effusion. The heart is sometimes dilated, at other times of normal size. In case of death on the second and third day there is usually less edema. In patients dead on the fourth day or later the lungs may be quite dry, but bronchopneumonia or pleurisy are usually present. In short, the earlier that death occurs the greater is the degree of pulmonary edema.

The blood usually exhibits definite changes; there may be a remarkable concentration, the hemoglobin percentage rising as high as 140 per cent., with a corresponding increase in the red cell count. This is brought about partly as a concentration from accumulation of its fluid in the lungs and partly as a sequel to shock and want of oxygen. Thrombosis is apt to develop, and minute, punctate hemorrhages are frequently found in the brain or other organs. The kidneys are apt to be enlarged and congested.

Removal to clean atmosphere is the most imperative treatment. Rest, the application of external warmth, and the administration of oxygen are of great importance. If cyanosis is marked the slow withdrawal of about 500 c.c. of blood often affords relief to the overburdened right heart, and may have some favorable influence on diminishing the

amount of fluid exudate in the lungs. Drugs are of little help; the various coal-tar products should be avoided since they are liable to bring on collapse. Cardiac stimulants, such as camphor, caffeine, or brandy are sometimes of value. Morphin is a dangerous drug to use when the respiration is seriously affected, and only small doses should be employed if absolutely necessary. The induction, by mechanical means, of vomiting is sometimes helpful by aiding in the discharge of fluid from the lungs. The elevation of the foot of the bed, for a few minutes at a time, may be employed with the idea of draining fluid from the chest. Food should only be given in fluid form, and sparingly in the acute stages.

Mustard Gas.—Di-chlor-ethyl-sulphid (CH_2ClCH_2)₂S is a liquid almost insoluble in water, slightly soluble in paraffin or vaselin, and particularly soluble in vegetable oils and fats.¹

It vaporizes very slowly at ordinary temperatures, and is very slowly decomposed by alkaline solutions, but is readily destroyed by dry chlorid of lime. The substance has only a very faint odor, usually likened to that of mustard or garlic, and it does not produce any immediately irritant effects. But after a delay of a few hours, the eyes, the mucous membrane of the respiratory passages, and the skin become severely inflamed. As far as life is concerned the action upon the respiratory organs is by far the most important, but the inflammatory condition of the skin and of the eyes frequently inflict great suffering.

On exposure nothing is noticed at first save the faint, though characteristic smell of the gas. After the lapse of two or three hours the eyes begin to smart and to water, and the conjunctivæ soon become reddened. The nose begins to run with thin mucus, as from a severe cold; sneezing is frequent. Nausea, retching, and vomiting occur at frequent intervals during the next few hours. The conjunctival irritation increases in intensity, the throat feels dry and burns; the voice becomes hoarse, and a dry cough develops. The skin becomes dusky, and reddened, and especially on the face and the neck the affected areas look as if they had been scorched, but they are almost painless; other portions of the body become similarly affected. This is followed by the development of small blisters in the involved areas. At the end of twenty-four hours a typical appearance is presented. The patient lies virtually blinded, with tears oozing between bulging eyelids over his reddened and blistered face; there is a constant nasal discharge and an occasional harsh, hoarse cough. Respiration is fairly normal; there may be frontal headache and marked photophobia. Death practically never occurs during the first twenty-four hours. During the second day the condition is aggravated by the development of larger blisters over the reddened areas, while the external genitalia become edematous and painful. Severe tracheitis and bronchitis are present, with abundant expectoration of muco-pus, sometimes containing actual sloughs from the inflamed mucosa. The temperature, pulse-rate, and respiratory rate are increased. Secondary infec-

¹ See chapter on Gaseous Poisons, p. 344.

tion of the necrotic mucous membrane soon leads to the development of bronchopneumonia, which frequently terminates fatally.

The most important changes are found in the respiratory tract; the mucous membrane is everywhere intensely reddened and covered with a thick yellowish-white pseudomembrane, the removal of which leaves a raw ulcerated surface. The lungs are slightly enlarged, but they do not exhibit the marked edema so characteristic of phosgene poisoning. In early death there will be found areas of emphysema alternating with collapse, and patches of petechial hemorrhage. After the second day patches of bronchopneumonia appear. In later death, septic, often confluent bronchopneumonia characterizes the picture. This may, of course, be associated with some edematous changes, but the edema here is not due to the gas but merely a part of the inflammatory picture. Microscopically there is marked necrosis of the tracheal and bronchial mucosa which is covered by a pseudomembrane; the bronchial tubes are frequently blocked with débris. The alveolar capillaries are engorged, many of the air-sacs contain desquamated epithelial cells; there is at first no edema, but later, as definite inflammatory conditions develop, more or less fluid is observed. The other organs show nothing characteristic.

In treatment removal to clean atmosphere and removal of contaminated clothing are essential. The eyes require frequent irrigations with warm, mild antiseptics, such as boric acid solutions, and instillation of liquid paraffin; cocain should be avoided, and the eyes should not be bandaged but should be protected from the light by dark glasses or a shade. Relief of the laryngeal discomfort is obtained by inhalation of steam charged with tinctura benzoini comp. and menthol. The skin is best treated with dusting powders; fatty ointments should be avoided. If bronchopneumonia develops this should receive the usual care. There are generally no after-effects from the poison, and recovery is usually rapid.

III. DEATH BY SUFFOCATION

The term suffocation was originally applied only to such cases of asphyxia as arose in consequence of disturbances operative internally and below the larynx (*sub, faux, -cis*). This meaning has, however, been entirely lost, and the common application of the term at present includes all cases in which asphyxiation results from any cause preventing the entrance of air into the mouth and nostrils, as well as any external obstruction to the respiratory movements of the chest and abdomen sufficient to prevent breathing, and also the toxic and mechanical effects of a number of gases preventing hematosis. For convenience, therefore, it may be considered from the point of view of either an external or internal insufficiency of the respiratory process.

(a) **Suffocation from External Causes.**—Instances of death from such cause are not very infrequent and may claim legal consideration as being the result of either homicide or accident, but practically never of suicide. The most common method of homicidal suffocation

is that known as "burking," so named from the famous Burke, who, with his comrade, Hare, in a number of instances accomplished murder in this manner. Here the victim, having been hurled to the ground, is held down by the weight of the murderer's body, which at the same time is sufficient to interfere seriously with the chest and abdominal respiratory movements. The criminal holds the mouth and nose shut with one hand closely applied, while with the other, unless otherwise required by the victim's struggles, he attempts to force the lower close to the upper jaw and thus aid in effectually closing the respiratory openings. When successfully applied, death generally follows in three or four minutes with all the usual symptoms of other forms of asphyxiation by external mechanical means. In these cases, while not necessary to the accomplishment of the murder, pressure upon the chest and abdomen doubtless hastens and makes more certain the fatal result. This same method of suffocation or smothering is sometimes wilfully, and frequently unwittingly, a means of infanticide. The parent, perhaps intentionally, perhaps unconsciously from drunkenness or from deep natural sleep, "overlies," as the term goes, the young infant occupying the same bed, completely stifling any attempt to cry and preventing all respiratory movements. Of course, in such instances the hand is not applied over the mouth and nose, the body of the parent generally performing the same office. Instead of the hand covering the respiratory openings, clothes, bandages, and similar objects may be applied for the same purpose. In a number of instances children have been known to have been smothered by being too closely and completely covered about the face. Mothers have been known to smother their infants by pressing them too closely to the breast when nursing. Smothering has resulted, too, by individuals falling in an unconscious condition in, or being placed purposely in, substances which occlude the mouth and nostrils, as mud, plaster, ashes, feathers, grain, or like material. Thus, intoxicated persons or epileptics have been known to have fallen face downward into mud and suffered death from suffocation. Infants have been buried alive in bran, ashes, feathers, and mud with the same result. Several instances are recorded where an insufficient access of air was permitted in making plaster casts of the features and bust, only the most energetic relief preventing death. Instances of suffocation in crowds, from the difficulty of accomplishing the chest and abdominal respiratory movements, are not infrequent when the pressure of the crowd is great; and this is materially aided, when the crowd is confined, by the effect of the excess of carbon dioxide and other products of exhalation.

Individual predispositions and resistances to this form of asphyxiation are identical with those already considered in connection with strangulation.

Symptoms.—The course of events in all these varieties of suffocation from agencies operating externally is similar to that mentioned in the discussion of strangulation, except that the effects of compression of the vessels and nerves of the neck and of violence to the tissues of the

neck and spinal cord do not enter. They may, therefore, be dismissed with brief enumeration. In cases where the suffocative obstruction is applied with suddenness and much violence immediate death may occur, as in strangulation, from cardiac syncope. Usually, however, a number of minutes elapse before death takes place, and in individual instances, where obstruction to respiration is incomplete, this period may be much lengthened. In ordinary cases, immediately following the application of the obstruction to the mouth and nostrils, there ensues a momentary pause in which the victim makes no effort to breathe. Then follows the more or less violent struggle for breath. The face becomes purple and almost black; the eyes protrude; there is energetic effort of the muscles of the nose, face, neck, and chest. The victim feels an overpowering demand for air; the head feels full and dully pains; the ears roar; the mind becomes extremely active. The pulse throbs violently and wildly; the whole body writhes in the violence of agony, and urine, semen, feces, and gas may be discharged. There come on rapidly a sense of loss of strength, relaxation, helplessness, indifference of result, and unconsciousness. The respiratory movements become weaker and weaker, and in two or three minutes cease; the pulse is lost more slowly, continuing to beat sometimes for many minutes after respiratory movements have failed. When the obstruction is of such a nature that it may enter the mouth and respiratory passages, as in case of mud or ashes, it may penetrate the nostrils and the mouth, may be swallowed and even be drawn into the larynx and trachea, when attempts at coughing and the reflexes from local irritation are likely to add to the unhappy situation. Only when the nature of the obstruction permits, and then merely at the beginning of the struggle for breath, are there efforts at outcry, limited to the short attempt at expiration. When the obstruction is incomplete, but the victim is unable to free himself, the respiratory efforts grow weaker and shallower, more and more irregular, accompanied by stertor, and finally cease; sometimes as much as twenty or thirty minutes elapse before the end is reached.

It is uncertain whether one should consider in this connection those cases said to die from suffocation from close confinement, as where a living person is entombed in a small space in a mine, or beneath a mass of dirt in some excavation; where a living person has been buried inclosed in a tight coffin and covered with earth; where, by some mishap or for some reason, an individual is shut up alive in a close closet or in a chest. The results seem but little different from those due to the direct occlusion of the respiratory openings, but the question must arise whether in reality death does not here take place from the accumulation of carbonic acid gas and possible but unestablished toxic respiratory excreta. There are few data to go by save those derived from persons rescued after confinement in mines or in such places as the famous "black hole of Calcutta" or the experiences of persons who have in crowds been confined in the holds of vessels for a number of hours with all the hatches closely shut; the symptoms of these persons, as already mentioned in the discussion of the effects of carbonic acid gas, uphold

the latter idea. In fact, when carefully regarded, one is tempted to give great weight to the view advanced by Fitz that all forms of mechanical asphyxiation are in reality instances of the effects of carbon dioxid accumulated with other deleterious principles in the blood from failure of expulsion through the lungs, the chemical and anatomic differences being circumstantial and the results of special conditions.

Postmortem Appearances.—As might be expected, there are here a number of appearances common to all forms of mechanical asphyxiation. The face and neck are usually darkly cyanosed, and there may be evidence of hemorrhage from the nose and mouth. The eyes are open and prominent, sometimes showing subconjunctival hemorrhages. The surface of the body is generally pale, occasionally showing points of ecchymosis here and there. On opening the body the blood is found dark and fluid, occupying the right side of the heart and the veins. The lungs are large, often showing emphysema, especially along the anterior border and edges of the base. They are not so deeply engorged as in some of the other forms of asphyxia, but are usually reddish in color. Beneath the pericardium, beneath the pleura, in the pia mater, as well as in the lungs, brain, and other viscera, small patches of hemorrhage, from the size of a pin-head to fifteen or twenty times as large, are very likely to be found. These patches are usually dark in color, round in shape, and contrast strongly with the surrounding tissue. There may be but few or they may be present in large numbers, and sometimes give rise to an almost granite-like marking of the lungs. Infants are especially likely to exhibit a large number of such markings when dying from smothering, and an important situation for their occurrence in such cases is the thymus body. The mucous membrane of the respiratory passages is usually red from congestion, and there is often more or less bloody froth accumulated upon its surface. The abdominal organs, especially the liver, kidneys, and alimentary walls, are congested, and similar engorgement is to be noted in the brain. Exceptions to these features may result from great suddenness of death, usually because of syncope.

When the victim has been smothered by the application of the hand over the mouth and nostrils, local signs of violence in the tissues compressed are likely to show. The nose is apt to be compressed; the cartilage of the septum is often broken; ecchymoses, and occasionally subcutaneous lacerations alongside the nose, upon the cheeks, and in the lips and gums, may be found. The inner surface of the lips often show signs of injury from pressure on the teeth. There may be more or less chafing and excoriation of the skin of these parts; just beneath the eyes, where usually the finger-tips of the murderer are applied, there may be more or less deep marks of nails. If the chin has been elevated forcibly, or the neck wrenched, in the efforts at complete closure of the nose and mouth, similar injuries may be inflicted upon the submaxillary tissues and even dislocation or fracture of vertebræ occur. When a cloth or mask of some pliable substance, such as rubber or wax, is applied to the mouth and nostrils, the local signs of violence are, as a rule, much

less marked than when the hand is directly applied; and it is possible, if a sufficiently soft, thick substance, as a pillow, is employed, that there will be absolutely no evidence of its contact.

A sign that should be sought for in such cases, although not generally mentioned in texts upon the subject, is the existence of recent rupture of the tympanic membrane. This is not of very rare occurrence in this form of asphyxia, taking place from the violence of respiratory effort, associated with the badly co-ordinated pharyngeal and laryngeal muscular movements in the period of struggle for breath.

In cases where the individual has been smothered by being purposely or accidentally, partially or completely, buried in sand, ashes, mud, and similar substances, as a rule the obstructing material will be found in the mouth, nostrils, esophagus, stomach, or larynx. It is drawn into the mouth and nostrils mainly by the struggle of the inspiratory efforts, and hence into the larynx and trachea. Its presence in the esophagus and stomach is the result of swallowing performed in order to relieve the mouth of the offending matter. It has been shown experimentally on lower animals that the air pressure in inspiration is sufficient, holding the animal up with head downward, in such substances as mercury and soft plaster, to carry the matter even into the bronchial tubes. Naturally it is impossible that any quantity of such material could find its way into the respiratory and alimentary tract any distance after life unless under great pressure. This is even more true than for submersion in water, yet, practically, the mouth and nostrils sometimes do in some way come to contain at least small amounts, even when the body is thus buried after death; and there are a few cases on record when, in experimental burial after death, even the larynx has been found to contain small bits of the surrounding substance. It is, however, fair to conclude, if such matter is found in considerable amount and is located in the larynx or lower, and, as swallowing is absolutely a vital performance, in the esophagus or stomach, that the occlusion of the respiratory openings occurred before death and that smothering actually did take place. When the suffocating mass is not sufficiently soft or light to enter readily the mouth and nostrils, naturally the sign indicated does not obtain. It may be possible to judge of the completeness of obstruction, however, in such material as mud by comparison of the imprint of the face in the mud with the features of the corpse. In such cases—as well as in any other form of asphyxiation—particular care should be taken to exclude influences such as opium or profound alcoholic intoxication, which are capable of producing congestions and fluidity of the blood postmortem and thus simulate, more or less closely, true asphyxia.

When suffocation has resulted from compression of the chest and abdomen or prevention of their respiratory movements, examination will usually reveal local injuries in these parts, either superficial or deep. On June 24, 1824, in a large crowd in the Champs de Mars, Paris, 23 persons thus met their deaths, and for a time were carried along as corpses in erect posture by the compact, singing mass. The degree of

compression may be appreciated when it is stated that in one-third of these cases there were fractures of the ribs, and in one case the sternum was broken. These cases all presented marked cyanosis of the face; in some cases there were ecchymoses beneath the conjunctivæ and hemorrhage from the nose and ears. On internal examination the blood was dark, fluid, and especially collected in the right heart and large veins. The lungs were deeply congested, as were also the abdominal viscera and the brain. In suffocation with less pressure upon the victim's body, as in a group of persons in an insufficiently ventilated space, there are necessarily absent such evidences of bodily injury, and, as a rule, there is less tendency to deep cyanosis about the face and neck and internal and external ecchymoses. In such instances the influence of carbon dioxid must be recognized. Compression of the chest and abdomen by the knees of a murderer or other force covering a comparatively small area is more likely to cause injuries, as bruises, fractures of the sternum and ribs, or lesions of the abdominal viscera, because of the concentration of the compressing force and the probability of its suddenness of application, than where the force is widely distributed, as by the weight of an overlying body or the lateral pressure of a crowd.

In all forms of smothering the tendency to formation of subpleural, subpericardial, and other hemorrhages is much less marked in adults than in infants, probably because of the weaker support of the engorged vessels by the surrounding tissues. In searching for these hemorrhagic patches in infants the thymus body should not be neglected, this apparently being a favorable situation for the lesion.

Treatment.—The provision of free, pure air, loosening of all clothing, removal of every source of compression and obstruction to the passage of the air to the lungs, artificial respiration, and cardiac stimulation constitute the main features of treatment. The mouth, nose, and larynx should be examined if any suspicion is entertained of suffocative matter having entered therein. Venesection in the neck and temples, friction of the surface, and the application of external heat may be required to aid in the re-establishment of circulation. Of the cardiac stimulants, nitroglycerin is especially advantageous. The proper care of local injuries should, moreover, be given as quickly as possible, when they seriously complicate the major difficulties. In case of fractured ribs, if the necessity for artificial respiration exists, the method of tongue traction of Laborde, already mentioned, is to be preferred.

Legal Consideration.—While in most cases it is easy enough from medical and circumstantial testimony to establish death from suffocation, cases necessarily occur where, from the insufficiency of one or both, it is quite impossible to declare absolutely that this was the lethal cause. At best it can be said that such instances are compatible with the suspicion of smothering. When the medical evidence includes, besides well-developed internal signs of asphyxiation (as dark fluid blood in the venous side of the circulation, congestions of the lungs, abdominal viscera, and brain and ecchymoses beneath the pleuræ, pericardium, and dura mater), also well-defined marks of local injury

about the chest and abdomen or about the mouth and nose, and more or less facial cyanosis and ecchymosis, it may be asserted, with reasonable certainty, that the victim was suffocated. The legal physician should have excluded, however, as far as possible, such influences as profound alcoholic or opium intoxication. In every case it is unwise to rely with any degree of exclusiveness upon this or that individual sign discovered; and the basis of opinion should always be made upon the entire group of manifestations encountered.

Aside from the evidences of violence, among the various internal signs of suffocation the existence of numerous ecchymoses is commonly regarded as of the highest suggestive importance. They are the result of capillary rupture in the latter period of asphyxiation, when the vascular pressure is at its height. They are usually quite small, varying in size from that of a common pinhead to that of a buckshot or a little larger, and are usually round and well defined. While most frequent in the subpleural and subpericardial tissues of the adult and in the thymus body of the child, they may have a very wide-spread occurrence and may be found in the peritoneum, abdominal viscera, brain, conjunctiva and retina, tympanum, mucous membrane of the mouth and respiratory passages, and in the skin, especially of the face. These ecchymoses may occur in any form of mechanical asphyxiation, but are most frequently and uniformly met in cases of death by smothering. Care should be taken to exclude the possible agency of various hemolytic diseases and poisons and the mechanical effects of different forms of cardiac diseases in the production of such suffusions.

Should there be reason to suspect that suffocation has resulted from occlusion of the mouth and nose by one or other means, the discovery of recent tympanic rupture should be regarded as of decided confirmatory value.

The value of evidences of injury, found upon the surface or in the structures underlying the applied force, about the mouth or in the thoracic wall is unquestioned; but the possibility of infliction of such injuries without actual destruction of life is also indubitable, and they are, therefore, to be accepted only in connection with the other evidences of smothering. So, also, with reference to the presence of some obstructing matter in the mouth and nose, identical with that on the exterior of these openings; while it must be strongly suggestive that the individual came to his death by smothering, for example, if a body is found partially or completely buried in mud or ashes and portions of such substances are discovered in the situations named; yet it must never be forgotten that it is possible, if the body is placed in similar surroundings after death, that penetration of the open mouth and nostrils by the semifluid or pulverulent matter might occur to some degree. The depth of the penetration and the amount of material should indicate here the probability; and in case the material in question has been found in the esophagus or below the glottis, there can be very little question as to the reality of death by smothering.

In fact, it is generally assumed that proof is complete in such

instances, particularly when the substance is found in the esophagus, as this would indicate the vitality of the victim when brought in contact with the matter swallowed. This feature may be insisted upon in such cases where it is declared in defense that the body, already dead from other, perhaps natural, cause, was, for some comparatively innocent motive, placed in such material; and the presence of the foreign matter in the esophagus may be regarded as surely demonstrating that life was not extinct when the body was thus disposed of. Of course, it in nowise excludes other influences of which there may be evidence contributory to death.

In fixing the responsibility, the question of suicide, although possible, practically never arises. Except in infants and adults disabled from some cause, *prima facie* inference is properly homicidal, and this should be maintained unless opposed by collateral testimony. In both these excepted groups, moreover, smothering is not an infrequent mode of homicide. The existence of distinct signs of violence of a character suggesting suffocating force is to be interpreted as indicating murder, unless reasonably referable to accident, but the absence of such signs does not preclude action for murder. The responsibility for the frequent death of infants from "overlying" is difficult to decide, but death from such cause can often be shown to be due, at least, to contributory negligence on the part of the caretaker. It is true that occasionally infants are born dead with fairly marked subpleural ecchymoses and fluid blood characteristic of suffocation; it is necessary, therefore, before asserting, in cases of young infants found dead with these signs shown upon autopsy, that legal suffocation had taken place, to establish, by observation of the size and appearance of the lungs and by floating a portion of pulmonary tissue upon water, that respiration had taken place before death and that the lungs had been inflated by air.

Confinement in coffins and entombment before death occasionally do occur, and suffocation from inclosure may cause or contribute to the cause of death. This is, however, practically impossible when proper inspection of the body has been made by a qualified person, and legal responsibility is thereby transferred to the inspecting physician or other officer. While exceedingly rare, the mere possibility should urge the advisability of such inspection. When, on the other hand, a body is found buried in an ash-barrel, privy vault, or other situation of similarly improper type, as is often the case with the bodies of the newly born, and presenting evidences of probable suffocative death, the responsibility for crime may be reasonably attached to whatever person may be shown to have thus disposed of the body, unless distinct evidence for his relief can be presented.

(b) **Suffocation from Causes Operating Internally.**—In a general sense all lesions impairing the receptive power of the lungs which may arise within the body, as well as the conditions preventing proper hematosis and convection of the arterialized blood to the tissues and its return to the lungs after performance of its function, should be included in such a category. Acute pneumonia, pulmonary edema,

tuberculous and other destructions of lung tissue, fibrosis of the lungs, and the various anemias, as well as various circulatory diseases, might properly be classified here; but in that they possess no medicolegal interest save as natural forms of disease, they cannot here receive attention, and consideration is limited to the results of inhalation of certain gases which, by blood alteration, are capable of interfering with the respiratory function. As already indicated, these should rather be regarded as intoxicants, and may, under special conditions, possess other and more rapidly fatal influences than that of blood destruction. Here may be included such agents as carbon monoxid, sulphuretted hydrogen, arseniuretted hydrogen, hydrocyanic acid, chlorin, nitrous vapors, as well as some of the anesthetic vapors. This important group is elsewhere separately considered in this work.

1. **Carbon monoxid (CO),**¹ carbonous oxid, also improperly known as carbonic oxid, is a product of incomplete oxidation of carbonaceous matter. It is a colorless, odorless gas, lighter than air. It is combustible, burning with a pale blue flame and producing carbonic acid gas, but it does not sustain combustion. This gas is produced in large quantities in the combustion of ordinary inflammable matter unprovided with free access of air; it does not develop in nature in any important amount. It arises from lime-kilns, brick-kilns, charcoal-kilns, from conflagrations without free supply of air, as in the interior of buildings, where it plays a most important part in cases of suffocation from smoke, from common charcoal and coke furnaces, from coal furnaces, and ordinary stoves when an insufficient supply of air is provided. Many of the modern explosives yield this gas in toxic quantities, especially when the explosions occur in confined spaces, as mines. After first lighting a coal-fire, and again when the incandescent coals, as the fire burns low, become smothered in ashes, this gas is formed in marked excess over the dioxid of carbon, and can often be seen burning with a light blue flame over the surface of the mass. When the whole mass is well aflame, with a fair draught, however, the carbon is more completely oxidized and the proportion of CO is much less than at the beginning and end of the process. Again, if, on account of insufficient opening for entrance of air at the bottom of the stove, or on account of the small amount of available oxygen in the small and badly ventilated room, the fire should burn but slowly, this underoxidized carbon gas is formed in large amount. Any imperfection of the stove-pipe or of the flue by which its escape into the room is possible, or by which its free passage to the exterior is impeded, must favor its collection in dangerous relation to the inhabitants of the apartment. In a small, ill-ventilated room, when the consumption of the air of the room by the fire has caused relative rarefaction, one can readily perceive how the deleterious product of the partial oxidation consequent upon small air-supply should pass from the stove out into the atmosphere of the apartment. The size and ventilation of the room enter as important

¹ Consult also the chapter on Gaseous Poisons, p. 296; also chapter on Industrial Toxicology, p. 791.

factors only in this latter relation, the proportion of the gas to the other elements of the atmosphere having little or no consequence. Only that portion of the gas in a room which enters into the blood has any effect, and if long enough time is given to the exposure, a small percentage will accomplish as much harm as a larger proportion in less time. In fact it is quite possible that the results may follow if the gas is inhaled in the open air and with it. In this feature it differs from the dioxid, which is mainly mechanical in its action, merely excluding a certain amount of respirable air, and requires a certain degree of proportionate accumulation before its effects can be produced. Finally, this gas is an important constituent of illuminating gas, especially that known as "water-gas," and is largely responsible for the fatal effects of its inhalation. "Natural" gas, however, contains usually little or no CO.

Suffocation by carbon monoxid has long been a favorite mode of self-destruction, and occasionally of homicide in certain countries, particularly in the district of the Seine in France. The victim usually shuts himself closely in a small room with a lighted brazier of charcoal, and becomes overcome by the gas arising therefrom, gradually and without particular discomfort. In 1891 the statistics show that in France as many as 848 suicides by this method occurred, nearly one-fifth of all the suicides of the republic for that year; and an enormous and steady increase is shown in each decade of the century. This frequency of suicidal method in France is doubtless entirely explicable upon the popular use of charcoal and coke furnaces for cooking, the ease and readiness with which the means of suicide can therefore be obtained, and the popular knowledge of the painlessness of the process. In our country and England suicide by this method is not common but increasing. Tramps, attracted by the warmth about the top of a lime-kiln, lie down close to the opening or on a board over it, and are overcome by the gas emanating from the combustion below. Suffocations occur from the entrance of the gas from a coal-fire in some way into the air of a room, and gradually the inhabitants, ignorant of their danger, are overcome. Ignorant or careless failure properly to turn off the stream of illuminating gas after extinguishing the light in some improper manner, as by blowing it out, often terminates the imprudent person's life in an hour or two. In this country when suicide is attempted by this type of suffocation, it is usually the result of purposefully turning on illuminating gas into the carefully closed room occupied by the subject. The noxious effects of CO depend upon the fact that after inhalation it forms rapidly, with the hemoglobin of the red blood-cells, a combination more stable than that resulting from the union of oxygen with this coloring-matter in the ordinary processes of respiration. The material thus formed, known as carbon-oxyhemoglobin or carbon oxid hemoglobin, being practically incapable of oxygen absorption, and the blood plasma likewise being unable, from greater or less occupation by the gas, to take in the respiratory oxygen, the process of hematosis is impossible and asphyxia results.

Symptoms.—The manifestations of intoxication by this gas depend much upon the rapidity of the process. A massive, gradual or chronic, form of intoxication may be present. The first type occurs occasionally on entrance into an atmosphere of ordinary illuminating gas, which contains from 4 to 30 per cent. of this gas, according to its kind, or into an atmosphere surcharged with carbon monoxid. The victim falls as if struck, and is dead within a few minutes, apparently from immediate exclusion of oxygen and before complete conversion of the hemoglobin into carbon oxid hemoglobin. There may be some specific action exerted by the gas also, but this is uncertain, and the process closely resembles the rapid asphyxiation by carbon dioxid. Convulsions are not infrequently present.

By far the most important train of events, from a legal point of view, occurs in the gradual asphyxiation resulting from more or less prolonged respiration in an atmosphere containing a relatively small proportion of the gas in question. The actual amount of gas in the air, and even the proportionate amount, is of little moment, and should not be insisted upon in any case, provided the time during which the gas was respired has been sufficiently prolonged. In other words, the results depend in this form rather upon the amount of carbon monoxid entering the blood, both hemoglobin and plasma, than that present in the air. This minimum fatal dosage can be determined only with the greatest difficulty, and then only approximately at best; but for an average human being it is probably within 1 or 2 grams.

The futility of quantitative estimation of the gas in any atmosphere in which death has occurred can be the more readily understood when one recalls that one may be killed in open air, where the percentage of gas is likely to be constantly varying, if close to its source, and that even in an inclosed room, where the gas is accumulating from a stove or furnace, it may continue to increase after the inhabitant has been destroyed. The proportions, as commonly given, are not only subject to such objections, but are quite too high. Briande and Chaudé, in their work on *Legal Medicine*, name as a lethal proportion 4 or 5 per cent., based upon certain experiments of Leblanc upon dogs killed by this gas in proportion of 5 to 1000. Experiments have shown, however, that dogs exposed for a long time—several days—are killed when a much smaller proportion exists—1 to 7000—in the atmosphere. This much can be said, however, that 4 or 5 per cent., and in isolated cases a smaller amount, of carbon monoxid in the atmosphere may prove rapidly fatal, but that much smaller proportions may, if continuously inhaled for a long period, also prove fatal, and that the absolute amount necessary to kill cannot be stated.

Individuals thus exposed to the gradual poisoning effects of carbonous oxid include the vast bulk of those brought to the attention of the legal physician dead from this gas; suicides from the use of charcoal furnace; imprudent and ignorant people accidentally killed by the fumes from badly ventilated stoves and furnaces; from kilns and by illuminating gas of one or other type escaping into the apartment. The

course of such a case is quite variable—from a half-hour or an hour to several days. For a time the victim feels an intense pain and pressure in the temporal regions; there is likely to be more or less tinnitus aurium, and sometimes there are ocular disturbances. He feels dizzy. There may be hallucinations or illusions. During this period of some minutes or an hour there is no especial difficulty of escape if such is desired and the danger realized. Presently, however, the effects of intoxication become more marked; the muscular power becomes progressively weaker until the victim is helpless. Nausea and vomiting are commonly present; sometimes there is general sphincter relaxation. Mentality gradually becomes dulled, and a decided tendency to sleep develops. The pulse at first is scarcely disturbed; it gradually increases in force and rapidity during the first period, but with the oncome of the symptoms of weakness soon loses its strength and becomes more or less intermittent.

The respirations, at first but little disturbed, become rapid, shallow, and often stertorous. Somnolence gradually passes into coma. The respiratory and circulatory functions become more and more insufficient, and finally the unhappy one dies. This last—comatose—period is likely to be longer in duration than either of the preceding ones. It lasts sometimes several days before death. It is possible, even after coma has been present for a considerable time, to resuscitate the patient. Should attempts at resuscitation be successful, the individual is generally for a long time more or less anemic, weak, and mentally dull or disturbed. Palsies of greater or less degree and of varying distribution have been encountered. Peripheral gangrene, pemphigus, herpes zoster, and disturbances of the special or general sensibility are recorded.

The chronic effects of carbonous oxid intoxication more frequently engage the attention of the general practitioner than of the legal physician. They occur in persons exposed more or less continuously to minute amounts of the gas, as those constantly immuring themselves in houses into which, on account of faulty gas-fittings, illuminating gas in small amounts gains access, or those whose occupations keep them more or less continuously in an atmosphere somewhat contaminated by the gas, as the workers about kilns, iron foundries, and gas manufactories. Bakers, launders, and cooks, who are for much of their time about red-hot ovens and stoves, through whose heated iron walls small quantities of CO_2 are apt to pass and in passage give up a part of their oxygen, are likewise subject to this variety of intoxication. The most constant and important symptom of this variety is the progressive type of anemia resulting from the gradual destruction of the blood and the widespread secondary symptoms of this state. Brouardel calls attention to occasional cholera-like attacks which are often met, especially in the last-named group, which, at least in part, he attributes to carbon monoxid poisoning. Experiments of Hava would indicate that in this form, where the process has been continued for months or years, the hemoglobin formation going on with sufficient activity to make life

possible, this substance may accumulate in the diffused hemoglobin of the muscles to such an extent as to make the mass inflammable in a condition which would explain instances of so-called "spontaneous combustion" if the element of spontaneity be eliminated.

Treatment.—While it is true that carbon oxid hemoglobin is more stable than oxyhemoglobin, and that ordinarily the blood of one thus poisoned fails to take up oxygen and become arterialized, nevertheless it is also true that in the presence of oxygen the carbonous oxid is gradually raised to the higher oxid, which is capable of disengagement from the blood. Free inhalation of oxygen, mixed with a small amount of CO_2 as advocated by Henderson, if necessary by forced respiration, should therefore be practised whenever possible; and at least in all cases artificial respiration should be insisted upon as a valuable measure. Venesection and replacement of that removed by directly transfused blood offers theoretically an ideal mode of dealing with the condition. Mere withdrawal of blood, unless indicated by existing engorgements of the venous circulation, is not advisable, since it lowers still further the already diminished oxygen-bearing power of the blood. Circulatory stimulation is demanded in nearly all cases, and hypodermic administration of rapidly diffusible stimulants, as ether and nitroglycerin, are often of decided value. When consciousness has returned, attention should be given to the lungs and respiratory mucous membrane, and the possibility of development of an inspiration pneumonia by the entrance of particles of the vomitus into the respiratory passages, as well as of bronchitis and tracheitis from the irritation by the gases or soot particles arising from combustion, be recognized. The various subsequent results, as the anemia and its consequences, are to be counteracted by careful and full nourishment and hygienic caution, as well as by medicaments indicated from time to time.

Postmortem Appearances.—While fairly constant, the postmortem appearances are subject to some variation, and these apparently depend largely upon the rapidity of the process and length of time after death when the autopsy is performed. There are, however, so many special conditions of environment and so many other agencies possible in co-operation with the carbonous oxid that it is not surprising that individual cases do not adhere to the usual rules. As a general thing the lips and face, as well as a greater or less part of the surface of the body, are of a life-like, rosy tint. But there are cases in which the face is pallid and all the surfaces except dependent parts at least blanched. These are usually those dead in a few moments from massive action of the poison, which are analogous to the syncopal deaths from other asphyxiating influences. Others, again, remind one of the effects of choking from the dioxid with swollen cyanotic faces and necks; and these also generally occur among the instances of massive intoxication. The rosy tint of the body surface is usually not uniformly distributed, but is best seen in large patches over the abdomen, thighs, chest, and in the dependent parts, where it may be more or less masked by ordinary postmortem hypostasis and lividity. A great variety of skin lesions

occur, chiefly of the bullous type; more or less severe jaundice is not infrequently present. The features are usually composed, the mouth partly open, the eyes open, and bright as in life. It is said that body heat and postmortem rigidity are of exceptionally long duration. On section, the most marked and invariable sign is the bright, cherry-red color of the blood, which is quite fluid and flows from even slight cuts. Ordinarily this character is maintained by the blood throughout the body, but in a number of cases, and these usually those dying rapidly, just as from carbonic acid choking, in which, particularly in some parts of the body, as in the abdominal veins, the blood is almost black and thick. It is probable that these persons die too quickly to permit the action of the carbonous oxid upon the entire volume of blood. The idea of the co-operation of the dioxid also in the atmosphere, along with the monoxid, and its selective action on the blood of these parts, is scarcely credible.

The peculiar appearance of the blood is perhaps the most characteristic sign of carbon monoxid poisoning, and should always lead to spectroscopic and chemical tests for verification and separation from the somewhat similar appearance due to other poisons, as cyanogen or its derivatives. The blood does not readily decompose and, if placed in a clean test-tube or vial and well stoppered, it may be kept for weeks or months in excellent condition for exact examination. Spectroscopically this blood gives rise to two bands, very like those of oxyhemoglobin, but narrower and beginning a little further to the right. Like the absorption bands of oxyhemoglobin, both these bands lie between the Fraunhofer lines D and E, but do not touch them; the A band is a little narrower and darker than the B band. A further difference between the spectrum of carbon oxid hemoglobin and oxyhemoglobin is this: While the addition of a reducing agent, as a drop or two of ammonium sulphid solution, to the blood will cause, in the latter, the two bands to merge into one broad band, the same effort will fail to modify the absorption bands of carbon oxid hemoglobin. A chemical test of simplicity, showing this particular change in the blood, may be performed, according to Katayama, as follows: Acetic acid and ammonium sulphid, with sulphur in solution, are added to the blood to be tested, when a clear rose-red color is produced; with normal blood a greenish-gray, sometimes with a slight red tint added, is produced. Kunkel's tannic acid test is likewise very simple to perform. It consists in diluting 1 c.c. of the suspected blood and 1 c.c. of normal blood (for purposes of control) with 5 parts of water. To each is added an equal part of a 5 per cent. solution of tannic acid and the solutions are well shaken. In the presence of CO the blood will remain more or less pinkish red, while the control blood assumes a dirty grayish-red color. The blood is mainly found in the venous side of the circulation, but may be met in both sides of the heart and in the arteries as well as veins. In case of spectroscopic examination of the dark blood occasionally found, the peculiarity of the carbon oxid hemoglobin spectrum is maintained.

The heart presents no especial features of interest; it is usually

found in a relaxed state. The lungs are somewhat congested, rather large, and of a brick-red color, best seen on section. They are likely to be somewhat edematous. The mucous membrane of the respiratory tract is generally bright red in color, but without much exudate, and is free from froth. Hemorrhages are not common, but subpleural spots similar to those seen in cases of mechanical suffocation are sometimes found. The abdominal organs are usually red and congested. The redness and possible presence of hemorrhagic spots may suggest the existence of an acute inflammatory process in the gastric and enteric mucous membrane, as from an irritant poison, which might mislead. The gastric and intestinal digestion is checked by this poison, and the degree of digestion of food in the stomach may afford some suggestion as to the time when the intoxication took place. Putrefaction is delayed, but not entirely, and after a time the development of intestinal gases causes sufficient pressure to force more and more red blood to the surface and thus extend the ruddy areas described. The most important anatomic changes occur in the central nervous system and consist of thrombotic softening of the thalamus and the lenticular nucleus. C. Wood believes that the anatomic peculiarities of the vessels in this region may have something to do with the ease with which they are damaged, for they are very long and thin, and without vasa vasorum. Under the influence of the enormous dilatation of the cerebral vessels, one of the first phenomena noted in connection with CO poisoning, the circulation may be sufficiently checked so as to permit the formation of a thrombus. Such thrombi have also been found in the smaller vessels elsewhere, and to them are probably due the minute hemorrhages which appear in the brain and the cord. In patients who recover from CO poisoning a number of obscure nervous symptoms may be referred to such vascular disturbances; and in subsequent autopsies the foci affected not infrequently show calcareous depositions and gliosis.

As already suggested, this gas is believed to be an important factor in destroying life in persons in buildings burning in the interior without free ingress of oxygen; many instances occurring where persons are found dead untouched by flame or heat and even with little evidence of having inhaled much smoke. Death is usually said to have been due to inhalation of smoke; but probably this gas and perhaps CO₂ are the important factors to be considered. In the bodies of those suffocated by the smoke of conflagrations, in addition to the above general features, the presence of particles of soot all along the respiratory tract should be noted. When these bodies are also exposed to the heat of the fire or direct flame, aside from the cracking of the skin and the baking and charring of the skin and flesh, small vermicular coagula, pointed out by Brouardel, are to be found in the vessels, especially in the lungs, thought to be due to the cooking of the hemic albumins.

Legal Considerations.—The determination of the actual cause of death by carbon monoxid is a matter of comparatively little difficulty on account of the well-marked signs found in most patients who have

thus perished, and by the spectroscopic and chemical examination of the blood. It is a frequent thing, after a murder, for the house containing the dead body to be set on fire by the murderer in order to conceal the crime by entire destruction of the corpse or by creating a belief that the victim was suffocated accidentally. Careful examination of the respiratory passages and blood of the dead should be at once made, and in the absence of the characters described, it may be stated with certainty that this latter suspicion is groundless and that death took place from cause other than suffocation by the smoke.

The determination of the question whether death was homicidal, suicidal, or accidental must rest almost solely upon collateral evidence. Homicides by such means are practically unknown in this country. Abroad, however, in France a few homicidal instances are upon record. Brouardel suggests that in cases of suspicion strong circumstantial evidence of complicity might be obtained by discovery of CO in the blood of the suspected person, the characteristic tests for which may be obtained a number of days after inhalation if a considerable amount had been inspired.

Questions involving the order of death have caused investigation as to the relative resistive power of males and females, of the adult and young, and as to the most fatal level in a contaminated atmosphere (raised, as upon a bed, or upon the floor). No constant rule may be stated; the best that can be said is that usually males succumb more quickly than females; that with more regularity children die earlier than adults, and that on account of the ready diffusion of the gases of combustion with the atmosphere of a closed room and with each other, position, elevated or low, has little or no influence upon the rapidity of poisoning. Precise answers to the proportionate amount of CO in the atmosphere upon the discovery of the body, or the amount of charcoal or other fuel required to produce a lethal amount or proportion of the gas, are of little value, as already pointed out, unless due attention is also paid to the probable duration of exposure, character of fuel and ash, form of stove or furnace, provision for ventilation, and other similar questions. Even then the sources of error possible are so great and the information so indefinite in its real import except where large proportions of the gas are found, that such features must remain only secondary.

Sulphuretted hydrogen (H_2S) acts similarly to carbon monoxid by forming a relatively even more stable compound with the hemoglobin of the blood (sulphemoglobin), and thus producing asphyxia by interference with hematosi. Its most characteristic change is produced on the blood, to which a dirty greenish tint is given. The gas may be determined spectroscopically and chemically, but a very important source of error arises from the possibility of generation of gas in putrefaction to cast an immovable doubt upon the results of estimation. It is met especially in the gas of privy vaults and in certain manufacturing processes and about sulphur springs, and possesses dangerously noxious powers.

Arseniuretted hydrogen (AsH_3), a gas occasionally accidentally inhaled in chemical laboratories, as in connection with the Marsh test in cases of arsenical poisoning, possesses dangerously poisonous properties. Its fatal consequences depend upon hemic destruction, apparently by changing hemoglobin into methemoglobin.

The symptoms of poisoning may be immediate or postponed for some hours, and are those of ordinary arsenic poisoning. Its course is usually more protracted, and may last a week or more. Besides the destruction of the blood-cells and production of anemia, it produces as a fairly constant lesion more or less well-marked fatty degeneration of various structures, and causes hemorrhages of varying severity.¹

¹ See chapters on Inorganic Poisons, p. 208; Gaseous Poisons, p. 347, and Industrial Toxicology, p. 790.

ALKALOIDAL POISONS

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ALKALOIDS are the main poisonous principles of plants. They include a large proportion of the known nerve poisons, and they act directly upon the nervous system, many of them acting through nerves upon certain muscles of the body. The several alkaloids are distinguished by the physiologic effect of each, in its individual power, upon different parts of the nervous system. The physiologic effects as obtained upon animals are limited according to the nervous organization in each species, and are more fully and surely obtained upon the developed nervous system of man.

The Chemical Character and Constitution of the Alkaloids.

—In classification the alkaloids are basal, electropositive in their ability to unite with acids and produce salts. Strictly speaking, an "organic base" may be a union of carbon with any element of the nitrogen family and with hydrogen preponderating over oxygen, if the latter be present. Ammonia is the inorganic type of the organic nitrogen bases, as phosphin and arsin are types of like organic bases formed by phosphorus and by arsenic. Pyridin is the structural type of the principal poisonous vegetable alkaloids and of the alkaloids which have the most marked chemical character. The pyridin nucleus, holding an atom of nitrogen with five of carbon in a closed chain, has all the stability of the fundamental benzene type, and has, besides, a special capability of additive combination. However complex the alkaloid, its electropositive polarity centers in the pyridin-like ring and in its nitrogen member. In the solanaceous alkaloids and in those of coca the structure is simply that of pyridin extended in side or cross chains of carbon to form a combined pyrrolidin nucleus. In the quinolin nucleus, which enters into the strychnos alkaloids, the pyridin is reinforced by a conjoined benzene ring. In some of the opium alkaloids the three-ring structure of phenanthren is united to the nitrogen nucleus, which differs from that of pyridin in the admission of oxygen instead of carbon in one of the six positions of the cycle. These closed chains are all of the six-membered type. Vegetable alkaloids are their highly complex derivatives. Such are the deductions drawn from the actual data of synthesis and of analysis, and they accord with the obvious character of these alkaloids, their clearly marked properties, and the distinctness of their deportment in analysis. Molecular individuality appears alike in their physiologic power and in their chemical activities.¹

¹ See Thatcher (*The Chemistry of Plant Life*, New York, 1921) and Annett (*Biochem. Jour.*, 1920, xiv, 618) for discussions as to the production of alkaloids in plants. For general discussions of the alkaloids see Schmidt, *Pflanzen-alkaloide* in *Biochemisches Handlexikon*, 1911, v, 1-7; Schmidt and Grafe, *Alkaloide* in *Handbuch der biologischen Arbeitsmethoden*, 1920, Abt. 1, Teil 9.

The chief alkaloids of the fungi and the so-called animal alkaloids or leukomains, as well as the ptomains or putrefactive bases formed during bacterial decomposition of vegetable or animal protein, are for the most part constituted with open chains of carbon as nitrogen bases. In some of these bases, however, nitrogen is found in closed chains of other than the regular type of six-membered rings, such as indol, which is of the type of pyrrol joined to benzene. Numbers of alkaloids, ptomains, and leukomains are as yet undetermined in chemical structure. Guareschi enumerates seventy ptomains and leukomains, among which twenty-six have been found to have open structure, and but seven have been shown to agree with the simple closed chain structures of the pyridin type. Of the latter, an example is the dihydrotoluidin, secondary base, obtained by Gautier and Mourgues from cod-liver oil. Putrescin and cadaverin are open-chain diamins of very simple constitution. The so-called alkaloids of tea and the other beverage plants are diureids, derivatives of purin ($C_5H_4N_4$), in which class belongs, also, the uric acid group of leukomains.

The element oxygen is found in the non-volatile alkaloids, and the structural relations of this element give the key to several peculiarities. Hydroxyl, especially if phenolic, gives solubility in the alkaloids. Ester formations, as in atropin and in a twofold way in cocain, render an alkaloid saponifiable as truly as a fat.

Identification in Analysis.—In respect to the bearing of structural chemistry upon fallacies of analysis in identification of the poisonous vegetable alkaloids, it is a reasonable conclusion that compounds of such remarkable chemical individuality ought to be identified by the analyst, and that he should be able to distinguish a vegetable alkaloid from a ptomain, at all events quite as surely as he can distinguish one vegetable alkaloid from another. Now when greater numbers of bases of vegetable and of putrefactive origin are becoming known, the danger of mistaking one for another is seen to have been greater than has been realized. But in this advance of chemical knowledge the resources of analysis are being enlarged and enriched as well. With these resources, when they are faithfully employed, greater precision is attainable in the determination of minute quantities of poisons, such as are recovered in postmortem analysis. Meanwhile the inherent limitations upon this recovery are more definitely understood. The new light shed upon the constitution of the organic bases reveals new means of identification and gives meaning to the detail of chemical tests.

Upon the important question of mistaking ptomains for vegetable alkaloids the conclusions of Guareschi, as given in his admirable work on this subject,¹ are presented in full in the following paragraphs:

Similarities of ptomains to plant bases make it very probable that

¹ Alkaloide mit besonderer Berücksichtigung der vegetabilischen Alkaloide und der Ptomaine, von Dr. Icilio Guareschi, Berlin, 1896. Guareschi and Mosso, *Les Ptomaines, Recherches chimique, physiologiques et médico-légales*, Arch. Ital. de Biologie, 1882-83, ii, 367; Ibid., 1883, iii, 241; Riv. di chim. med. e farm., 1883, i, 54, 92, and 121. Guareschi, *Gaz. chim. ital.*, 1887, xvii, 503.

before the researches of Selmi ptomains have been frequently mistaken for alkaloids in medicolegal cases. This conjecture increases in probability from the fact that formerly many chemists considered it to be sufficiently conclusive of poisoning to have extracted from the already putrefied intestines a poisonous alkaline-reacting substance giving all the general reactions of the alkaloids. Today it is not so difficult to avoid that fallacy, although the discovery of cadaver alkaloids places a considerably higher responsibility not only upon the judgment but also on the knowledge and experience of the chemist. On the other hand, the chemist of today must guard against the other extreme, that of allowing the vegetable alkaloids to leave the field altogether to the ptomains—attributing to the presence of the latter observed reactions which really are those of plant alkaloids present in the organism. *All vegetable alkaloids, with a few exceptions, can be characterized as such by their chemical and physiologic behavior, so as to be recognized in the presence of ptomains. A careful and experienced worker of today will not confound a vegetable alkaloid with a ptomain that is known and worked out, since, in spite of the great number of the ptomains, none has been observed to give reactions uniform in all points with any plant base.*

An exception to this general statement may perhaps be made in case of poisoning occasioned by muscarin, and certain actively poisonous bases of the pyridin and hydropyridin series, as the last-named bases also occur among products of putrefaction. In these cases the proof of the occurrence of poisoning from analytic results alone is not only very difficult, but in the majority of cases impossible.

Moreover, special caution in expression of opinion is needful in all cases where the amount of the vegetable alkaloid extracted from portions of the body is too small to yield all the characteristic chemical and physiologic reactions. The same is true when the alkaloid cannot be obtained in purity, but remains mixed with ptomains and extractive matters. In all these cases it is practically impossible to draw definite and unobjectionable conclusions from analytic results.

Another consideration especially important from a chemicolegal point of view is the possibility of changes taking place in the composition of alkaloids under analytic treatment, such as those resulting in so-called amorphous alkaloids, some of which are insufficiently examined. The possibility of such changes makes it the strongest duty of the chemist fully to find his bearings upon the properties and reactions of all such plant-bases as colchicin, delphinin, cannabin, oleandrin, pseudo-curarin, lobelin, the alkaloids of hops, and others which are known only in the amorphous condition (Guareschi).

It has been stated that the chemical tests, especially the color-reactions for certain vegetable alkaloids, may be simulated so closely by certain bacteriologic products (ptomains) that it becomes impossible to distinguish with certainty between them. While it is undoubtedly true that many basic products of more or less toxicity are produced by bacterial activity, yet it is quite as true that these derivatives do not show exactly the same chemical or color reactions, identical in all

respects, as those given by the vegetable alkaloids. As stated above, one should, perhaps, make an exception of such putrefactive products as pyridin, pyrrol, indol, etc., inasmuch as these bases might be the cause of a true exogenous poisoning and, at the same time, be detected in the cadaver as putrefactive endogenous products.

It is evident, therefore, that the work of the toxicologist and that of the bacteriologist must overlap to a certain extent. With the advance of our knowledge of these scientific fields, it has become an accepted fact that the absolute recognition of a case of "ptomain poisoning" rests more largely upon the isolation and identification of a specific micro-organism than upon the chemical detection of uncertain basic products of bacterial action.¹ These ptomains often obscure the chemical tests for certain alkaloids and, occasionally, give reactions so closely analogous to those of certain true alkaloids that doubt may be cast upon the findings of the analyst. Although this has been attempted in several capital cases, it should be capable of absolute contraversion. Admitting the possibility of such influences, the analyst should take special precautions in the purification of his residues and should make his identification tests side by side with specimens of known alkaloids. The reactions shown by ptomains vary in color or sequence of color from those given by the pure alkaloid in some one or more of the characteristic tests. Further, even though the chemical reactions may be so closely simulated, physiologic tests will often be widely at variance. The analyst should be constantly on his guard with reference to pseudo-reactions, and should insist that his report be based, unequivocally, upon true chemical and color reactions as well as upon the biologic tests. In this way he will fortify himself against the possibility of making uncertain deductions. Thorough familiarity with the color reactions, shown by the various alkaloids will prevent any confusion as to the identity of a specific residue. This question of interference of ptomains with the identification of certain alkaloids will be discussed in some detail under the head of the specific alkaloids.²

Properties of Vegetable Alkaloids.³—In respect to physical state these substances may be divided into: (1) Non-volatile alkaloids: very numerous, composed of carbon, hydrogen, nitrogen, and oxygen, usually colorless or white solids, melting when heated and usually subliming with partial decomposition, but inodorous and incapable of distillation unchanged. (2) Volatile alkaloids: comparatively few in number, composed of carbon, hydrogen, and nitrogen, without oxygen, for the most part liquid when free as bases, abundantly odorous and capable of distillation unchanged, even at ordinary atmospheric pressures. Nicotin, the odorous and poisonous principle of tobacco, is an example of the second division, as quinin is of the first division.

Both classes are capable of neutralizing ordinary acids, without

¹ See section on Food Poisoning, p. 813.

² See Rosenau, *Med. Clin. North America*, 1919, ii, 1541.

³ See Zeehuisen, *Arch. f. exp. Path. u. Pharm.*, 1920, lxxxvi, 342, for a general discussion of the physical properties of a large number of alkaloids.

the liberation of hydrogen or formation of water, with the production of salts of the alkaloids, such as a sulphate or hydrochlorid.

Solubilities.—*In Water.*—When free from combination with acids, the greater number of vegetable alkaloids are counted as insoluble in water—that is, their solubility in water is very slight. Thus, it is stated¹ that strychnin is soluble in 6420 parts of water at 25° C. (77° F.) or in 3100 parts of boiling water. Cocain is reported to dissolve in 600 parts of water at 25° C. (77° F.). On the other hand, the ordinary salts of alkaloids, such as the sulphate, nitrate, acetate, or hydrochlorid, dissolve quite freely in water. The solutions are neutral to litmus and most other test-papers. Strychnin sulphate requires but 32 times its weight of cold water to dissolve it; morphin sulphate requiring about half as much of the same solvent. It is in correspondence with the facts just stated that in ordinary aqueous solutions of the salts of the alkaloids the addition of any caustic alkali (short of excess) will cause an immediate precipitation of the uncombined alkaloid. Excess of the caustic alkali will redissolve such precipitates of alkaloids in some instances (especially atropin, cocain, and morphin), but not in others, so that the effect of an excess of alkali is a means of distinguishing alkaloids from each other, a reaction seldom delicate enough to be useful with very small quantities. The effect of alkalis upon the ester-like composition of the so-called saponifiable alkaloids is not an immediate effect, and, though a reaction to be regarded, it is one likely to escape observation unless made a subject of inquiry.

Solubility in Alcohol.—In general, both the free alkaloids and their salts are soluble in ordinary alcohol with considerable abundance, and in proportions varying with the strength of the alcohol. Alkaloidal salts usually dissolve in alcohol more abundantly than do the free alkaloids; therefore, a partial precipitation of alkaloid is obtained in some cases by adding alkali to an alcoholic concentrated solution of alkaloidal salt, but this reaction is uncertain. Absolute alcohol is valuable as a solvent to separate alkaloids from various tissue-substances. This separation from protein and other matters *requires to be made gradually with increasing strengths of the alcohol*, or else very thorough washing of the finely divided precipitate, to avoid waste of the alkaloid by its retention in the matters coagulated by the alcohol.

Ether and Chloroform as Solvents.—These are the best known of the so-called immiscible solvents, those not miscible with water and separating from aqueous solutions in which they have been mixed by shaking. Neither chloroform nor ether, however, is entirely immiscible with water. The free alkaloids differ from each other as to solubility in ether and in chloroform, and these solvents have been somewhat used as a means of separating alkaloids from each other. The scheme introduced by Dragendorff in 1867 is the most elaborate plan for such separation, five or six immiscible solvents being used.² But these sol-

¹ Pharmacopeia of the U. S., 9th rev., 1916.

² For description of the Dragendorff Process, see p. 54.

vents are more in use to effect a separation of whatever alkaloid be in hand from matter other than alkaloids, which is also done in Dragendorff's process; and in this use the analyst avails himself especially of this fact, that the sulphates, hydrochlorids, and other salts of the alkaloids are sparingly soluble in the immiscible solvents with a very few well-known exceptions (colchicin, cinchonin, papaverin, narcein, and hydrastin). This fact was first made available by Otto in 1856, in his modification of the method of Stas for the extraction of alkaloids in toxicology. For example, from an acidulous aqueous solution containing strychnin, chloroform will dissolve out and remove whatever matters are soluble in this solvent, leaving practically all of the alkaloid as a salt in the watery solution. Now the liquid is made alkaline and treated with the chloroform, in which the free alkaloid readily dissolves, and a distinct step in purification is taken. By the repetition of these stages of treatment the alkaloid is gradually purified. In the complex scheme of Dragendorff, already mentioned, all his immiscible solvents are employed successively in acid and then in alkaline solution, the aqueous liquid being shaken out with each solvent, which is left to separate and then drawn or siphoned off. In this connection it is to be remembered that the alkaloidal salts are not *entirely* insoluble in the immiscible solvents, so that traces of these may be extracted from acidulous solutions by such solvents. This is, not infrequently, of great moment in toxicologic examinations, as one may lose most, if not all, of his alkaloid by the preliminary shaking out of acid solutions with the various solvents.¹ Ether and chloroform are used also upon solid residues, stirring to dissolve, as well as in an "extraction apparatus" and in other ways in the course of analytic work.

Other Immiscible Solvents.—The benzene (benzol) of coal-tar distillation, petroleum ether, amyl-alcohol, acetic ether, acetone, are used in the same general ways stated for ether and chloroform, according to the adaptation of each.

General Reagents for the Precipitation of Alkaloids.—Alkaloids agree in promptly forming certain inorganic combinations, such as double salts and perhalids, and a few organic combinations, all insoluble in water, so that they are instantly thrown down from aqueous solutions of alkaloidal salts on adding the proper reagent. In order to determine the presence of an alkaloid in the purified residue obtained in the extraction processes outlined in the section on General Principles of Toxicology, general reagents, known as alkaloidal precipitants, are employed. It is to be stated that many, if not all, of these reagents, likewise, precipitate protein material and derivatives, so that the purification processes must be very carefully conducted before one is in a position to draw any conclusion from the results obtained with these alkaloidal precipitants. In performing the test for the presence of alkaloids, by the use of these general precipitants, one should remember that great care must be taken to conserve his material, as the amounts of residues recovered in the extraction processes are usually

¹ See chapter on General Principles of Toxicology, p. 61.

small. The method recommended by Gadamer¹ is very efficient and reliable. A small portion of the dried residue, obtained in the extraction process, is treated with a single drop of dilute sulphuric acid (1 : 50) and slightly warmed to bring it into solution. By means of a fine-pointed glass rod transfer a portion of this solution to a small watch-glass resting upon a black background and then add a small drop of the reagent. If an alkaloid be present, a precipitate will be observed at the point of contact of the two liquids or even throughout the mixture. The most serviceable and reliable of these reagents are the following, but it should be noted that many others have been advocated.

1. Iodin in Solution of Potassium Iodid (Wagner's Reagent²).—A decinormal solution of iodine with sufficient potassium iodid (12.692 gm. of purified iodine and 18 gm. of potassium iodid dissolved in 1 liter of distilled water). For qualitative uses about 1 part of iodine and 2 parts of potassium iodid in water to make 100 parts of solution. Applied in acidulated solutions, not alcoholic, and added in excess. The precipitates, of varying shades of dark brown to black color, are periodids, and are usually flocculent and amorphous, although they may become crystalline. The higher periodids, by excess of reagent, are more stable than the lower periodids.³ By action of sodium thiosulphate solution the alkaloidal precipitate is dissolved, the periodid being reduced to a hydriodid. When the latter is made alkaline and treated with an immiscible solvent, the pure alkaloid is recovered.

2. Potassium Mercuric Iodid Solution (Mayer's Reagent⁴).—For qualitative use by adding to solution of mercuric chlorid a little more than enough of solution of potassium iodid to dissolve the colored precipitate at first formed (13.576 gm. of mercuric chlorid and 49.8 gm. of potassium iodid dissolved in 1 liter of distilled water). For quantitative purposes the solution should be a N/20 one, containing 6.788 grams of mercuric chlorid and 25 grams of potassium iodid dissolved in 1 liter of distilled water. This reagent is invariably to be applied in an acidulous solution, and in absence of alcohol or acetic acid. The precipitates are yellowish-white in color, and are crystalline or become so on standing. On treating the precipitate with stannous chlorid, then adding caustic potash to alkaline reaction and extracting with an immiscible solvent, the free alkaloid is obtained. van der Heyde⁵ recommends this reagent as the most delicate and reliable for detecting atropin in small quantities of blood-serum.

3. Potassium Cadmium Iodid Solution (Marmé's Reagent⁶).—Prepared by saturating a boiling concentrated solution of potassium iodid with cadmium iodid and adding an equal volume of cold saturated solution of potassium iodid. For qualitative purposes this may be

¹ Lehrbuch der chemischen Toxicologie, Göttingen, 1909, p. 482.

² Bouchardat, *Compt. rend.*, 1839, ix, 475; R. Wagner, *Zeitschr. anal. Chem.*, 1861, i, 102; 1865, iv, 387.

³ Prescott and Gordin, *Jour. Amer. Chem. Soc.*, 1898, xx, 709; *Proc. Amer. Phar. Assoc.*, xlvii, 357.

⁴ *Ztschr. f. anal. Chem.*, 1863, ii, 225; see also Peset, *Ann. d. hyg.*, 1909, xi, 289.

⁵ *Jour. Lab. and Clin. Med.*, 1922, 7, 280.

⁶ *Compt. rend. Acad. d. Sc.*, 1866, lxiii, 843; *Ztschr. f. anal. Chem.*, 1867, vi, 123.

made by dissolving 10 grams of potassium iodid and 5 grams of cadmium iodid in 100 c.c. of distilled water. This reagent is applied in acidulous solution in the absence of alcohol. It produces precipitates which are, for the most part, white and flocculent, although some become crystalline. These precipitates are soluble in excess of the reagent and in alcohol. On decomposing with alkali and extracting with the proper immiscible solvent, the free alkaloid may be obtained.

4. Potassium Bismuth Iodid Solution (Dragendorff's Reagent¹).—Prepared like Marmé's reagent, substituting bismuth iodid for the cadmium iodid. This reagent is applied to acidulated solutions of alkaloids in the absence of ether and amyl alcohol, producing orange-red precipitates, which are often crystalline.

5. Phosphomolybdic Acid (De Vry's or Sonnenschein's Reagent²).—This reagent is prepared as follows: 150 grams of crystallized ammonium molybdate are dissolved in 1 liter of distilled water, and this solution is gradually poured into 1 liter of concentrated nitric acid. To this mixture a warm solution of sodium phosphate is added until no further precipitation of ammonium-phospho-molybdate occurs. The yellow precipitate is filtered off, washed with water, and dissolved in a hot solution of sodium carbonate. The solution is evaporated to dryness and ignited at a low red heat until all ammonium salts are volatilized, the residue is moistened with nitric acid and again ignited. This product, which is sodium phosphomolybdate, is then dissolved in ten times its weight of a mixture of one volume of concentrated nitric acid, and nine volumes of distilled water to obtain the final reagent. This reagent is a close precipitant of the alkaloids, forming yellowish, usually amorphous precipitates with most alkaloids, although some may become crystalline on standing. If ammonia be added to the precipitates, in case of certain alkaloids having a reducing action, the precipitate turns blue or dissolves with a blue color. Such action occurs with aconitin, atropin, berberin, codein, colchicin, coniin, morphin, nicotin, eserin, etc.³

6. Phosphotungstic Acid (Scheibler's Reagent⁴).—This is prepared by dissolving 100 parts of sodium tungstate and 60 to 80 parts of sodium phosphate in 500 parts of distilled water and adding nitric acid till the reaction is distinctly acid. It is used in a manner similar to Sonnenschein's reagent and gives related reactions with the alkaloids, which are quite delicate. The alkaloids may be recovered from their phosphotungstates in the same manner as from their phosphomolybdates by mixing the moist precipitates with potassium or sodium carbonate and extracting rapidly with strong alcohol.

7. Bromin in Hydrobromic Acid (Wormley's Reagent⁵).—Aqueous

¹ Pharm. Ztschr. f. Russl., 1866, v, 81; Die gerichtlich-chemische Ermittlung der Gifte, 4te. Aufl., 1895, p. 155.

² De Vry, Jour. de pharm., 1854, 3 s., xxvi, 220; Sonnenschein, Handb. der gerichtl. Med., 1869, p. 317.

³ Henry, Allen's Commercial Organic Analysis, 4th ed., 1912, vi, 188.

⁴ Ber. d. d. chem. Gesellsch., 1872, v, 801; see also Heiduschka and Wolf, Schweiz. Apoth. Ztg., 1920, lviii, 213, 229.

⁵ Micro-Chemistry of Poisons, 2d ed., 1885, p. 642.

hydrobromic acid is saturated with bromin. This is a close precipitant of most alkaloids and is especially valuable for microchemical work. The precipitates are mostly yellowish and amorphous, although they occasionally show characteristic crystalline forms (see Atropin).

8. **Tannic acid**, in freshly prepared aqueous solution, precipitates the alkaloids with more or less completeness, the precipitate being in some cases prevented or dissolved by acidulation with mineral acids.

9. **Picric acid (Hager's reagent¹)** in water solution gives beautiful precipitates, many of them crystallizable, with a number of the alkaloids. Nelson and Leonard² believe that the more commonly occurring alkaloids may be tentatively identified under the microscope by the form or habit of their picrate crystals prepared under standard conditions.

10. **Picrolonic Acid (Knorr's Reagent³)**.—This substance, which is 1-p-nitro-phenyl-3-methyl-4-nitro-5-pyrazolon, was found by Knorr and his students, Braun and Zeine, as well as by others to be very valuable as an alkaloidal precipitant owing to the marked insolubility of the compounds formed. The reagent is prepared, according to the method of Braun, as follows: 600 c.c. of 90 per cent. nitric acid (specific gravity 1.49), prepared by diluting 540 c.c. of the strongest fuming nitric acid with 60 c.c. of water, were kept cold with ice-water in a wide-mouth bottle; 200 grams of methyl-phenyl-pyrazolon were added, 1 gram at a time, the mixture being mechanically stirred all the while and the temperature being kept below 15° C. (59° F.). Each addition of substance causes a vigorous reaction attended with escape of red fumes. At the end of the addition of the methyl-phenyl-pyrazolon, the mixture is stirred for thirty minutes and then the crystalline mass is collected upon a small porcelain disk covered with asbestos, is freed from acid by suction and is washed successively with dilute nitric acid and then with water. This crude product of trinitro-methyl-phenyl-pyrazolon is now saponified by the addition of 1500 c.c. of 33 per cent. acetic acid (about six times the weight of the crude product), the mixture being mechanically stirred in a beaker on the water-bath. The saponification is complete in twenty to forty minutes, the temperature of the mixture not being allowed to exceed 60° C. (140° F.). A mass of light yellow, flocculent crystals replaces the reddish-yellow compound and fills the liquid. This crude picrolonic acid is thrown onto a Buchner filter, freed from acid by suction, well washed with water, and then ground in a mortar with 150 grams of crystallized sodium carbonate, carbon dioxid being given off and the yellow sodium salt formed. This salt is pressed out and crystallized from a mixture of 3 volumes of strong alcohol and 1 volume of water. The salt is then decomposed

¹ Ztschr. f. anal. Chem., 1870, ix, 110; Ibid., 1881, xx, 415; see also Popoff, Le Laboratoire de Toxicologie, 1891, p. 203; Warren and Weiss, Jour. Biol. Chem., 1907, iii, 327.

² Jour. Amer. Chem. Soc., 1922, 44, 369.

³ Knorr, Ber. d. d. chem. Gesellsch., 1897, xxx, 909; xxxii, 732 and 736; see also Braun, Inaug. Dissert., Jena, 1899; Steudel, Ztschr. f. physiol. Chem., 1903, xxxvii, 219; Ibid., 1905, xlv, 157; Zeine, Inaug. Dissert., Jena, 1906; Warren and Weiss, Jour. Biol. Chem., 1907, iii, 327; Matthes and Rammstedt, Ztschr. f. anal. Chem., 1907, xlvi, 565; Arch. der Pharm., 1907, cexlv, 112.

with concentrated hydrochloric acid, the acid being warmed on the water-bath and the sodium salt being added in small portions. The picrolonic acid separates as a yellow, mealy powder. This is thrown onto a porcelain disk covered with asbestos, freed from acid by suction, and washed with water to remove the remaining acid and sodium chlorid. This is the finished product and is used as an alkaloidal reagent in the form of a saturated alcoholic solution (each cubic centimeter containing about 0.021 gm.). The precipitates formed by picrolonic acid are yellow or red, and are easily decomposed by heat. To recover the alkaloid from its picrolonate, it is necessary only to warm the latter with dilute sulphuric acid, which causes the alkaloid to pass into solution and precipitates pale yellow picrolonic acid. By extracting this mixture with acetic ether, the aqueous solution retains the alkaloid, while the picrolonic acid passes into the acetic ether. Characteristic precipitates are yielded by picrolonic acid with coniin, nicotin, strychnin, brucin, morphin, codein, atropin, quinin, and hydrastin, while aconitin, cocain, and caffein do not furnish definite compounds. It is especially valuable in the purification of strychnin residues.

11. Salts of Heavy Metals, Such as Platinum and Gold Chlorid.—These salts form double salts with alkaloids, which are difficultly soluble and are usually crystalline. Determination of the platinum or gold content of these double salts yields some quantitative figures of value.

Use of General Reagents for Negative Tests.—There are various substances not alkaloids precipitated from their aqueous solutions by the general reagents just described. The final solution obtained in the processes of extraction of alkaloids from the tissues of the body, though carefully purified by action of alcohol and of immiscible solvents from any remaining traces of ordinary protein matters, will generally give a slight turbidity, due perhaps to leukomains, under action of potassium mercuric iodid or of phosphomolybdic acid, and sometimes under action of iodine. If a quite concentrated solution so obtained give only a slight turbidity with such a general reagent, this result may be accepted as negative for the presence of a poisonous alkaloid, unless in too minute a quantity to be precipitated. It will be usually advisable to apply such special chemical or physiologic tests as are of greater delicacy than the tests by general reagents.

More decided precipitation by a general reagent, applied to a well purified extract from tissues or organs of the body, certainly calls upon the analyst to apply special tests for poisonous vegetable alkaloids with the utmost care and with economy of material. But such is the liability of precipitation of ptomains or of leukomains in unusual abundance under action of the general reagents, and such the possibility that some kind of "animal extractive matter" besides the bases, possibly approaching a protein composition, may have escaped removal in the processes of purification, that *even a considerable precipitate by a general reagent cannot be taken as conclusive of the presence of a vegetable alkaloid, still less of a poisonous one.* In analyses of food materials or medicines

a precipitate by a general reagent has more positive bearing than in the analysis of tissues, but even here the analyst must not base very much upon the reaction of a general reagent alone.

Special Chemical Tests and Color Reactions.—While the above general precipitants may be used as group reagents to a large extent, they do not yield precipitates which are sufficiently characteristic for purposes of absolute identification. Fortunately, practically all of the alkaloids, with which toxicology is concerned, show special chemical and color reactions, which permit of their differentiation. While, perhaps, no single reaction is sufficient to warrant a conclusion as to the identity of a certain residue, yet it may lead to the use of other tests, which collectively, are conclusive. Although some of these color tests yield somewhat similar results with different alkaloids, careful comparison will usually reveal slight variations which become important in toxicological work. The variations noted may be either in the initial color, the final color, or in the sequence of color noted. In the application of any such test the analyst must rely chiefly upon his own observation and experience of the reaction with a known sample of the alkaloid, taken in such minute quantity as would best represent what might be recovered in analysis. It is further essential that the separated alkaloid be in as pure a condition as possible, as impurities or admixtures of alkaloids may prevent the formation of the characteristic coloration, may obscure the reaction, or may give results which are so similar to those of the suspected alkaloid as to lead to error in deduction.

Certain of these reagents react with so many of the alkaloids, although the colorations observed may be varied, that they may be regarded, in a sense, as general reagents. Others yield, in many cases, such a definite color or sequence of color tints that they must be considered special reagents, even though wide variations may be noted when they are applied to different alkaloidal residues. It is to be emphasized that a single color test is, rarely, conclusive as to absolute identity of a certain alkaloid, owing to possible influences of impurities. It should be insisted upon, where possible, that all of the more important and well-established reactions shown by the pure alkaloid be obtained with the purified residue extracted from the tissues, if one is to give an unequivocal opinion as to identity. It is not infrequently impossible to conform to this rigid scientific requirement, owing to the small amount of material isolated. In such cases, the analyst must be extremely guarded in his deductions and not overestimate the value of his limited scope of examination.

While these color tests are described in the text as the colors or sequence of tints observed by the normal eye of the analyst, it must be remembered that lack of perception of certain colors (color-blindness) by the analyst does not preclude the possibility of recognition of an alkaloid and the establishment of its identity. If the colors observed by him are identical, when the suspected residue and a like portion of known pure alkaloid are tested side by side, it is evident that the

PLATE 5.



Atropin with Vitali's test.



Brucin with nitric acid followed by stannous chlorid.



Mixed alkaloids of gelsemium with sulphuric acid and ceroso-ceric oxid.



Morphin with ferric chlorid.



Strychnin with sulphuric acid and ceroso-ceric oxid, or manganese dioxid.



Veratrin (mixed alkaloids) with sulphuric acid.

ALKALOIDAL COLOR REACTIONS

NOTE.—It is practically impossible to imitate by the lithographic art every shade of color produced in alkaloidal reactions, and consequently, while the above chart gives an excellent idea of the colors obtained, they are not in every respect absolutely correct.

substances are the same, even though the shades of color observed are widely at variance with those stated by the text as characteristic for the specific alkaloids.

Certain of these reagents will be discussed in a general way at this point, while the more specific tests will be detailed under the separate alkaloids. It is to be remembered that every precaution should be taken to purify the alkaloidal residue before applying any of these special tests. The best method of observing the color reactions of the alkaloids and suspected residues is to apply a drop of the reagent by means of a fine-pointed glass rod to a minute particle of the solid residue placed on a porcelain plate or in a flat porcelain dish. Excess of reagent, as well as of alkaloid, is to be avoided, as the most characteristic results are obtained with small quantities.

The reagents used in the various color tests for alkaloids are quite numerous, many of them being often very unsatisfactory owing to the presence of impurities. Some of these are, in a sense, general, while others are, strictly speaking, special reagents. The color reactions of alkaloids may be classified, according to Henry,¹ as (1) those produced by dehydrating agents, such as concentrated sulphuric acid; (2) those given by oxidizing agents not of themselves yielding colors, such as nitric acid, chlorine, or sulphuric acid, and oxidizing agents, such as potassium dichromate, manganese oxid, lead oxid, ceresoceric oxid, etc.; (3) those yielded by oxidizing agents which themselves give a colored product by reduction, such as iodic acid, and reagents containing chromic, molybdic, tungstic, and vanadic acids; (4) colorations produced by special reagents, such as ferric chlorid.

1. Concentrated Sulphuric Acid.—*No color*, or only a faint straw shade is given by pure aconitin (which is rarely obtained), atropin, cocain, codein, scopolamin, hyoscyamin, gelsemin occasionally shows a yellow followed by brown), morphin (often light red if reagent is impure), nicotin, quinin, quinidin, and strychnin.

Yellow, orange, or brown colorations are yielded by berberin, colchicin, delphinin, gelsemin, and lobelin. Yellow tints followed by red or violet are noted especially with the alkaloids of veratrum.

Red, purple, or violet colors are obtained with impure aconitin, apomorphin, brucin (due to impurity of nitric acid in the reagent), impure cocain, coniin, impure gelsemin, narcotin, and physostigmin.

2. Concentrated Nitric Acid.—*No coloration* is noted with pure aconitin, atropin, cinchonin, coniin, gelsemin (may show yellow or green if impure), quinin, and strychnin.

Yellow tints are obtained with impure aconitin, berberin, codein, gelsemin, morphin (may show red), narcotin, and veratrin.

Red, purple, or violet colors are given by impure aconitin, apomorphin, berberin, brucin (deep red), and physostigmin.

3. Fröhde's Reagent.—This is prepared by dissolving 1 or 2 mg. of molybdic acid in 1 c.c. of chemically pure sulphuric acid. Other directions specify higher proportions of molybdic acid, but these lessen

¹ Allen's Commercial Organic Analysis, 4th ed., 1912, vi, 198.

the distinctiveness of the test.¹ This reagent must be freshly prepared just before use as it is gradually reduced on standing with production of colored oxids of molybdenum. While this reagent gives colorations with many alkaloids, its most distinctive reaction is with morphin.

No color is produced with atropin, cinchonin, coniin, hyoscyamin, nicotin, scopolamin, and strychnin. *Yellowish colorations* are observed with aconitin and colehicin. *Reddish shades* are noted with brucin and veratrin. *Bluish colors* are given by codein and morphin (purple fading to violet, then dirty green, yellow, and finally to faint pink). *Greenish shades* are yielded by apomorphin, berberin, and quinin.

Many other reagents, such as those of *Mandelin*,² *Selmi*,³ *Brociner*,⁴ *Luchini*,⁵ *Sonnenschein*,⁶ *Lafon*,⁷ and *Mecke*,⁸ are often used. These consist of oxidizing substances in solution in concentrated sulphuric acid. As these yield characteristic reactions only with special alkaloids, their discussion will be deferred. Likewise, such special color tests as those of *Vitali*,⁹ *Husemann*,¹⁰ *Marquis*,¹¹ *Pellagri*,¹² *Brande*,¹³ and *Lefort*¹⁴ will be discussed under the special alkaloid to which they are applicable.

Biologic Tests.—Physiologic tests are those used for the detection of a poison by studying its action upon living plants or animals, these "biologic objects" serving, therefore, as living reagents. These methods may be employed both for qualitative and quantitative determination, although more frequently for the former, the poison being usually administered in aqueous or very slightly acidulated (acetic acid) solution. The animals most frequently used are frogs and white mice, although the larger animals, such as rabbits and guinea-pigs, not infrequently yield more characteristic results with certain alkaloids, while the human subject may serve more advantageously in detecting physiologic properties of certain alkaloids, such as aconitin and atropin. It is evident that the intensity and rapidity of the observed action will depend upon (1) the amount of the poison employed; (2) the method of application, whether intravenously, subcutaneously, or per os; (3) upon the size and weight of the animal employed, and (4) upon the type of animal used.¹⁵ Examples of these and their most

¹ Fröhde's original communication (*Ann. der Chem.*, 1861, cxx, 188) called for 0.01 gram of sodium molybdate in 1 c.c. of concentrated sulphuric acid. See, however, *Arch. der Pharm.*, 1866, clxxvi, 54.

² *Jahresber. ueber Pharmacog. Pharm. and Toxikol.*, 1883-84, xlv, 766.

³ *Ber. d. d. chem. Gesellsch.*, 1878, xi, 1692.

⁴ *Jour. de pharm. et de chim.*, 1888, 5 S., xviii, 204; 1889, xx, 390; 1890, xx, 468.

⁵ *Ztschr. f. anal. Chem.*, 1886, xxv, 565.

⁶ *Berl. klin. Wchnschr.*, 1873, x, 310.

⁷ *Compt. rend. Acad. Sc., Paris*, 1885, c, 1543.

⁸ *Ztschr. f. offentl. Chem.*, 1899, v, 350.

⁹ *Jour. de med. chir. et pharm.*, 1880, lxxi, 66, 161, 167, 279, 382.

¹⁰ *Ann. der Chem. und Pharm.*, 1863, cxxviii, 305.

¹¹ *Arbeit. der pharm. Inst. zu Dorpat.*, 1895, xii, 132.

¹² *Gazz. chim. ital.*, 1877, vii, 297.

¹³ *Ann. der Chem.*, 1839, xxxii, 270.

¹⁴ *Jour. pharm. et de chim.*, 1861, xl, 97.

¹⁵ See Fühner, *Nachweis und Bestimmung von Giften auf biologischem Wege*, Berlin, 1911.

Alkaloid.	Mayer's reagent.	De Vry's reagent.	Concentrated sulphuric acid.	Concentrated nitric acid.	Concentrated sulphuric acid with oxidizing agents, as potassium bichromate, manganese dioxide, lead oxid.	Fröhde's reagent.	Specialty valuable tests for identification.
Aconitin.	Yellowish-white non-crystalline precipitate.	Yellowish-white precipitate.	No color when pure. Yellow to red when impure.	No color when pure. Yellowish or red when impure.	Slight yellow colorations, becoming light green on standing.	Yellowish or orange.	Crystalline form, m.p. and percentage of gold in chloraurate. Biologic test.
Atropin.	Yellowish-white crystalline precipitate.	Yellowish; turns blue with NH_3 .	No color.	No color.	Lemon yellow changing to green.	No color.	Character of the precipitate with gold chlorid. Vital's test. Biologic tests.
Cocain.	Yellowish-white crystalline precipitate.	Yellowish-white precipitate.	No color when pure. Reddish if impure.	No color.	Light yellow, changing to orange and finally green.	No color. Slightly yellowish on standing.	Character of double chlorids of gold and platinum. Selzer's test. Biologic tests.
Codein.	Yellowish-white crystalline precipitate.	Brownish-yellow precipitate.	No color at first. Becomes blue on long standing.	Yellowish in cold. Reddish if heated.	Light yellow, changing to brown and finally greenish.	Yellowish, deep green, finally blue.	Ferric chlorid. Mecke's tests and Tunnann's tests.
Colchicin.	No precipitate in dilute solutions. Yellowish-white in concentrated.	Yellowish-white precipitate.	Lemon yellow color.	Violet red, changing to green and then to yellow.	Light yellow, showing greenish streaks as oxidizing agent is drawn through. Becomes dark yellow and then light yellow.	Yellow solution, changing to yellowish-green and back to yellow.	Nitric acid and ferric chlorid tests. Barillot's test. Biologic test with mice.
Gelsemin.	Yellowish-white crystalline precipitate.	Yellowish-white precipitate.	No color when pure. If impure, yellow followed by brown.	No color if pure. May show yellow or green if impure.	Reddish purple or cherry red without initial blue or violet. Liquid assumes green or bluish-green tint.	Purple or reddish-violet.	Concentrated sulphuric acid with oxidizing agents. Biologic tests.
Morphin.	Yellowish-white crystalline precipitate.	Yellowish-white precipitate.	No color when pure. May get light red due to nitric acid in reagent.	Orange. May show slight reddish tone.	Green.	Purple, fading to violet, then dirty green, yellow, and finally pink.	Fröhde's, Marquis', Husemann's, Leffort's, and Pellagra's tests.
Physostigmin.	Yellowish-white crystalline precipitate.	Yellow amorphous precipitate.	No color.	No color or slight reddish yellow.	Light yellow with faint greenish tint.	Slightly reddish-yellow.	Rubrescin test. Ammonia test. De Silva's test.
Strychnin.	Yellowish-white crystalline precipitate.	Yellowish-white precipitate.	No color.	No color.	Blue to purple, then violet, reddish, rose-pink, finally yellow.	No color.	Bitter taste. Fading purple test. Crystalline test.
Veratrin.	Yellowish crystalline precipitate.	Yellowish-white precipitate.	Yellow; soon orange, green fluorescence, red, carmine red.	Yellowish, changing to red.	Lemon yellow, changing to brownish-red, then deep brown.	Yellow, changing to reddish.	Sulphuric acid test. Cane-sugar test. Biologic test.

important uses will be found in the text for strychnin, atropin, and aconitin. Their relative value is stated in each case. *Each test, chemical or biologic, is to be valued upon its merits, judged from all known data in the experience of chemists, pharmacologists, and practical analysts.* It cannot be said that chemical evidence is insufficient without physiologic data in the examination for all poisonous alkaloids. In analysis for aconitin the physiologic test is the main reliance; in search for atropin it is perhaps the best dependence; in the work for strychnin it is strong confirmation; in examining for cocain it is one of several tests; while among the means of identification of several other alkaloidal poisons physiologic methods have only a subordinate place.

The **delicacy of tests for alkaloids** as a class is not exceeded by the delicacy of tests for inorganic poisons. The least quantity of an alkaloidal poison which is sufficient for its positive identification when it is taken by itself in well-known tests is very small when compared with poisonous doses, or, in general, even with medicinal doses. The chief task of the analyst, however, is to obtain the poison by itself through its removal from other matters.

Separation from Animal Tissues.—Notwithstanding the peculiar individuality of the vegetable alkaloids, shown both in their physiologic effects and their chemical constitution, already remarked upon on page 417, they still share in the frailty of all organic compounds. Their separation, in amount comparatively minute, from overwhelming masses of organic matter in tissues and foods, is a task far more delicate than the extraction of inorganic poisons. No method which involves the corrosion or chemical alteration of tissue-substances would be possible. All the processes are dependent upon the action of solvents and of reagents which convert the alkaloids into their salts or other combinations, or else liberate them from like combinations previously formed. Under the head of Solubilities (page 420), also of General Reagents (page 421), the principles are stated upon which the various methods of separation of alkaloids from tissues have been elaborated.

Directions for the Separation of Alkaloids from Tissues.¹—These are given in different places in the text with the purpose of adapting the process to the character of the alkaloid, as follows:

Under Morphin.—A process advisory for an alkaloid that must be especially guarded against oxidation.

Under Atropin.—The treatment recommended when the alkaloid must be guarded against hydrolysis (saponification). Applicable to cocain, and with additional precautions to aconitin, as specified.

Under Strychnin.—A process proposed when the alkaloid is to be guarded against contamination with remaining impurities, and will bear treatment of comparative severity for separation. The treatment with hot concentrated sulphuric acid, however, is admissible with no other alkaloid than strychnin.

¹ Consult also p. 52 et seq. in section on General Principles of Toxicology.

Under Nicotin.—A method for a volatile alkaloid, to be guarded against waste by vaporization.

Chemists of experience in the work will very properly adopt such outlines of methods as have been found by them to be most satisfactory and secure. The principles of separation are to be ever borne in mind. The skilful analyst will modify whatever outline he uses so as to accomplish separation and purification gradually, step by step, prudently guarding against waste, as required in quantitative work.

Precipitation of Alkaloids with Lloyd's Reagent.—Instead of following the general methods of extraction of alkaloids, as outlined in various portions of the text, Lloyd's reagent may often be advantageously employed to precipitate these basic substances, and thus obviate many difficulties which frequently arise in toxicologic work. Further, the use of this reagent minimizes the possibility of saponification, which may occur with the usual methods of extraction.

Lloyd's reagent (as shown by his Letters Patent, No. 1,048,712, December 31, 1912¹) is a highly hydrated aluminum silicate in colloidal form. It is derived from fuller's earth and consists, according to the analysis of Waldbott,² of water, 17.41 per cent.; silica, 55.30 per cent.; aluminum oxid, 9.82 per cent.; ferric oxid, 14.18 per cent.; calcium oxid, 1.58 per cent.; carbon dioxid, undetermined. When this insoluble reagent is added to an acidulated aqueous or alcoholic solution of an alkaloid, the particles of hydrous aluminum silicate ("colloidal sponges" of Lloyd) grasp the alkaloid or its salt and carry it down in the meshes of the magma. According to Lloyd, to the water side of this reagent may be attributed its attractive energy; at least, the alkaloidal affinity depends on the influence of the water present. "Almost I would venture to coin for the most potent form of this reagent the term 'colloidal water.' The addition of the alkaloid to the reagent liberates this water and destroys the colloidal condition of the mother sponge, the product, which before was a slime, settling as earth does in water, carrying with it the alkaloid by adhesion." The tenacity with which this reagent holds the alkaloid is shown by the fact that even strychnin is no longer bitter, although the combination is physiologically active. Lloyd's Canadian patent (203,257, August 24, 1920) calls for the use of hydrous magnesium silicate.

This reagent is employed as follows: Extract the finely hashed tissue with acidulated water or alcohol, as in the usual processes, employing low temperatures when the easily saponifiable alkaloids are suspected. Filter the acidified extract and wash residue thoroughly. Add to this clear filtrate a few grams (1 or 2) of finely powdered fuller's earth made into a thick paste with a little water. Shake thoroughly and allow the earth to settle out. Filter, collecting the entire sediment on a small filter, washing with water until there is no reaction for the acid originally in the solution. Allow the residue to dry slightly and

¹ See also Lloyd, Amer. Jour. Pharm., 1916, lxxxviii, 217.

² Jour. Amer. Chem. Soc., 1913, xxxv, 837.

transfer it to a flask or, preferably, a separatory funnel; add a little water, alkalinize with ammonia, and shake out with the proper immiscible solvent. Withdraw the solvent and re-extract two or three times. Evaporate the combined solvents to obtain the alkaloid, which is usually in an amorphous form, but may become crystalline, and is quite pure.

While this method certainly causes complete withdrawal of the alkaloid from its solution, it is by no means proved that the recovery of the alkaloid from the colloidal magma is actually quantitative. Indeed, Gordin and Kaplan¹ have shown that morphin and strychnin, at least by the methods followed, are not completely removed from the precipitate by extraction of the alkalinized residue with immiscible solvents. If this is true, the method will not find ready adoption for more than qualitative purposes.

Analyses for Alkaloidal Poisoning Before Death.—In cases of patients under treatment, when poisoning with an alkaloid is suspected, the urine should be subjected to strict analysis for the poison or securely retained for such analysis, as should also the vomit or washings of the stomach if they can be obtained. If aconite poisoning be suspected, the saliva likewise may be analyzed. (See the text under the head of Deposition in the Body for the several poisons, and Atropin, Case 11; Morphin, Case 23; Strychnin, Cases 14, 18, 20.) Portions of food or of medicine under a reasonable suspicion of being poisoned should also be retained under seal.

A Control Analysis.—If the operator would ascertain just what is really accomplished by a given process of separation from tissues, or by the process he has decided to use, he can do no better than to conduct, at the same time, and in all respects with the same conditions, the given process upon the same quantity of like tissues, in about the same stage of decomposition, in which a weighed quantity of the poison in question has been intimately mixed. The quantity of the poison should be minute enough by careful calculation not to be in excess of what would be present in a real case of poisoning. It must be recognized that a brief mechanical mixture of the dissolved alkaloid with the comminuted tissue material or other organic mass will not ensure as great a difficulty of separation as that which is met with in a case of poisoning. Therefore, the records of results of analysis of the remains of poisoned animals are of material advantage; and experiments where the tissue substance has been charged with a known (minute) quantity of the poison, either by administration to the animal before death or by intimate admixture to dead tissues, and the whole then allowed to putrefy, are therefore more conclusive in their bearing upon analyses made some weeks or months after death. In such cases the experimental putrefaction should be conducted in the same conditions of exclusion or limited access of air, and of temperature as near as can be, as those of the burial of the remains under investigation.

¹ Amer. Jour. Pharm., 1914, lxxxvi, 461; see also Clowes and Walters, Jour. Amer. Med. Assoc., 1920, lxxv, 655.

Extraction of Alkaloids from Tissues Not Without Inherent Waste.—This has been proved by experiment. It may be understood from the laws of physics. Solubility and insolubility are but relative terms which we use for differences of degree. A coagulum or undissolved residue will retain by adhesion some fraction of what is dissolved in the filtrate, however this fraction may be divided by washings. There is "analytic error" even in inorganic analyses, and when dealing with colloidal matter in masses, several tens of thousands times larger than the crystalloidal poisons to be recovered, the unavoidable "analytic error" may exceed the ratio of the quantity of the poison, or leave less than what is needful for its identification.¹

Results of Experimental Analysis for Alkaloids.—In experiments with Prescott,² Kirchmaier found that strychnin was not uniformly recovered, even to a qualitative extent, from the blood of animals poisoned with it, nor from organs of the body. From the blood of the heart and of the general circulation the poison was obtained by analysis in 2 cases out of 4, $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.016 gm.) of the alkaloid having been administered hypodermically to cats two to eight minutes before death and the examination commenced half an hour after death. From the liver a trace of the poison was recovered in only one out of six of the same series of experiments, one in which $\frac{1}{8}$ grain (0.008 gm.) of the alkaloid was injected five minutes before death and analysis commenced half an hour after death. The kidneys were analyzed in the six experiments with a negative result. When $\frac{1}{32}$ grain (0.002 gm.) of the alkaloid was introduced into the stomach of the animal eleven minutes before death, twelve hours afterward analysis of the stomach gave evidence of the poison. But when $\frac{1}{60}$ grain (0.001 gm.) of the alkaloid was given by the stomach twenty minutes before death, analysis of this organ immediately after death yielded no indication of the poison.

Further on this subject, see Cases 14 to 20 under Strychnin; Case 11 under Atropin; Cases 23, 67, and Analyses 1 to 7 under Morphin.

Experiments to Guard Against Fallacies in Analysis.—These may be brought to bear upon a given qualitative test or a given method of separation from tissues, or upon both.

Nine portions of putrefied matter, representing as many organs of an animal body buried forty-five days in a container, "a tight wooden box," in March and April, were extracted first by alcohol acidulated with acetic acid, later with hot amyl-alcohol, along with other treatment, and the final extracts, as prepared for qualitative reactions, in no cases gave any indication of morphin by Lefort's test, made by iodic

¹ Control Analyses and Limits of Recovery in Chemical Separations, A. B. Prescott, Chem. News, London, 1885, liii, 78. In the systematic execution of a given process of separation of strychnin from muscular tissue, with 50 gm. of the latter, the loss of the alkaloid was about 0.0004 gm. Therefore, in separating strychnin from 1 pound of the tissues, about $3\frac{1}{2}$ mgm. of the alkaloid were lost. In this experiment the waste of the alkaloid, in separating from 1 pound of tissues, was over one thousand times the least quantity necessary for identification when the alkaloid was taken alone in a qualitative test. See also Homberger and Munch, Jour. Amer. Chem. Soc., 1916, xxxviii, 1873, for a discussion of the recovery of morphin.

² Contributions, Chem. Lab., University of Michigan, 1883, ii, 91.

acid followed by ammonia. In all the cases, however, the ordinary test with iodic acid and starch gave the blue color of liberated iodine.¹

To find at the same time the trustworthiness of Lefort's and Fröhde's qualitative tests, and of the method of extraction from tissues presented under the head of Morphin, and to determine the liability of interference from products of tissue putrefaction when air is excluded, the following procedure was instituted: About $2\frac{1}{2}$ kilograms of finely chopped ox-liver were placed in a large bottle (*a*) securely stoppered with a perforated cork connected with a bent glass tube. The cork was sealed with paraffin and the outer end of the glass tube was allowed to dip into a cistern of mercury, thus excluding all communication with the outside air. Putrefaction was now allowed to go on, in a warm room, for about fifty days. Gas was given out during the earlier part of the decomposition. Into another bottle (*b*) another $2\frac{1}{2}$ kilograms of finely chopped ox-liver were placed with 0.52 gram of morphin intermixed, about 1 part in 5000, and this bottle was sealed, connected, and set aside with bottle (*a*) for putrefaction thirty-five days. The contents of bottle (*a*) in duplicate portions, in one with the process of extraction detailed under Morphin, and in another portion with Kippenberger's proposed extraction method, gave final residues that, under the Lefort test by iodic acid, also under Fröhde's reagent, in each portion brought absolutely negative results. On the other hand, the contents of bottle (*b*), that containing morphin when set aside, in two portions, with the first above specified extraction method, in a parallel Lefort test by iodic acid, gave a clear mahogany color, a strong indication for morphin. No indication of the alkaloid was gained from the extraction process of Kippenberger.²

Again in 1896, to prosecute the same inquiry under conditions of actual animal poisoning, when the poison is physiologically distributed among the tissues, with putrefactive changes in confinement from the air after death, Smith and Prescott proceeded as follows: Of morphin 23 grains (1.5 gm.) were given through the mouth to a dog of about 15 kilograms weight; two hours afterward the animal was killed with an anesthetic, the body placed in a box made of sheet-iron, and the box sealed hermetically, this being on February 20th. In the following month another dog of about 30 kilograms was killed with an anesthetic without any administration of morphin, and the body sealed up the same as the other one. The two boxes were buried on March 20th, in a wooden case, under about 3 feet of soil. On May 8th, after about seven weeks' burial and about ten and a half weeks of inclosure of the body containing morphin, the two boxes were exhumed. The box containing the larger body, the one sealed up later, had burst from gas pressure within and its contents were in a state of decomposition more advanced than that of the smaller body. From each body the stomach, intestines, and liver were taken together in analysis by

¹ D. L. Davoll, from work done in consultation with Prescott, University of Michigan, Jour. Amer. Chem. Soc., 1894, xvi, 805-807.

² H. T. Smith, 1894, in work under Prescott's observation, University of Michigan.

the method given under Morphin for separation from tissues, and also by the process proposed by Kippenberger. In the final result each one of the putrefied extracts from the body of the animal poisoned with morphin gave distinct reactions for morphin in Fröhde's test and in Lefort's test, but gave no reaction with the ferric-chlorid test nor with sulphuric and nitric acids. The purified extracts from the body of the animal not poisoned, in parallel portions, gave no reactions for morphin in the tests just named. With Kippenberger's process the final residues failed to yield any reaction for morphin from the body of the poisoned dog, and gave no appearance of a morphin reaction with any of these tests in the extracts from the body not poisoned.

Precautions Against Impurities in Reagents.—In addition to the proper tests of purity, to which the analytic chemist must subject all his reagents and solvents before taking them into use, advantage can be taken of a blank analysis for control to exclude fallacious results from any source, and misleading reactions in the final tests. At any rate it is necessary to be assured that the immiscible solvents yield no residues that can react with the agents employed in testing for alkaloids, and that the residues of all solvents and reagents together give negative results in the tests that are depended upon.

Quantitative Determination of Alkaloids.—From what has preceded it is evident that the estimation of the absolute amount of alkaloid in the tissues examined in any given case of alkaloidal poisoning must be, at best, only an approximate one. If the final residue be not sufficiently purified a positive error arises; while the attempt to procure a perfectly pure alkaloid leads to more or less loss of substance, thus introducing a very decided minus error. The analyst must report his findings as so much alkaloid actually recovered and be content with this approximate result, never going so far as to state that the amount reported represents the exact quantity of alkaloid present in the tissues. It is not always possible to obtain quantitative values for the alkaloids owing to the very small amount sometimes isolated, yet in every case of toxicologic importance, some statement regarding quantities isolated must be given.

The most satisfactory, and indeed, the usual method of determining the quantity of alkaloid extracted is the ordinary *gravimetric* one. This consists in actually weighing the amount of pure alkaloid isolated from a given quantity of tissue. The amount of tissue employed in the extraction should be an aliquot part of the total weight of the special tissue. Having determined the amount of alkaloid in the tissue extracted, a simple calculation yields the total quantity in the whole organ, assuming, of course, that the alkaloid is equally distributed throughout the organ.

As a check upon this gravimetric determination, the residue after weighing may be dissolved or softened by the addition of about 1 c.c. of neutral alcohol or ether, and a *volumetric estimation* of the alkaloid present may be made as follows: Add a known volume of N/100 sulphuric acid and a little water to the dissolved alkaloidal residue.

Warm slightly if necessary to insure complete solution of the alkaloid and titrate the excess of acid present, using N/100 sodium hydrate solution as the neutralizing agent, and cochineal, methyl-red or iodeosin as an indicator. Subtraction of the amount of alkali solution added to produce a neutral reaction from the amount of N/100 acid originally employed yields that amount of acid combined with the alkaloid. Each cubic centimeter of N/100 acid thus combined represents $\frac{1}{100000}$ of the molecular weight of the alkaloid to be determined expressed in grams.

While many other methods have been introduced with the view of permitting quantitative estimations, few of them have proved acceptable or reliable. Thus, the volumetric methods employing precipitation of the alkaloid with Mayer's, Wagner's, or Dragendorff's reagents do not give clear-cut end reactions, especially in presence of impurities. A slight modification has been introduced by *Thoms*,¹ who decomposes the precipitate, formed with Dragendorff's reagent, with a mixture of sodium carbonate and hydrate, extracts the free alkaloid with the proper immiscible solvent, evaporates in a weighed dish and thus determines the weight of purified alkaloid. This method yields satisfactory results, but is much more cumbersome than the usual gravimetric method outlined above.

Similarly, *Matthes and Rammstedt*² precipitate the alkaloid with a 0.1 normal alcoholic solution of picrolonic acid (26.4 gm. per liter) as a yellow or red crystalline material. This precipitated alkaloidal picrolonate is collected in a weighed Gooch crucible, washed with a small amount of water, dried and weighed. This method yields reliable results, but it is not to be recommended on account of the difficulty of obtaining or preparing the pure picrolonic acid. The method of *Prescott and Gordin*³ and the later method of *Gordin*,⁴ which is based upon the fact that periodids of the alkaloids, when precipitated from aqueous solution by iodo-potassium iodid or by Mayer's reagent in presence of acids, always contain one equivalent of combined acid for every molecule of monacid alkaloid, yield varying results of sufficient degree to prevent general adoption. (In this connection, see *Kippenberger*.⁵)

Period of Detection of Alkaloidal Poisons.—The alkaloids present much variation among each other in their power to resist decomposition during the putrefaction of tissues in which they are deposited. No alkaloid can be affirmed to be indestructible under these conditions. Probably the resisting power of alkaloids has been underrated, owing to defective analyses. The records of analysis in actual cases, the data upon which we must mainly depend, are given under the proper sub-head for each alkaloid.

¹ Ber. d. d. pharm. Gesellsch., 1903, xiii, 240; 1905, xv, 85.

² Ztschr. f. anal. Chem., 1907, xlv, 565; Arch. der Pharm., 1907, ccxlv, 112; see Knorr, Ber. d. d. chem. Gesellsch., 1897, xxx, 909; 1897, xxxii, 732, 738; also Warren and Weiss, Jour. Biol. Chem., 1907, iii, 327.

³ Jour. Amer. Chem. Soc., 1898, xx, 329, 712, 722, 724; Arch. der Pharm., 1899, ccxxxvii, 380.

⁴ Ber. d. d. chem. Gesellsch., 1899, xxxii, 2871.

⁵ Ztschr. f. anal. Chem., 1903, xliii, 101.

ACONITE AND ACONITIN

General Description.—Aconitin represents the poisonous alkaloids of the drug aconite, the three or four other bases present in aconite being either non-toxic or much less so than aconitin.¹ The drug consists of the root, sometimes the leaf, of *Aconitum napellus* (monkshood) and other species of *Aconitum*. Aconitin itself, of the ascribed formula $C_{34}H_{47}NO_{11}$ (acetyl-benzoyl-aconin), is one of the most concentrated poisons known, and at the same time is a very unstable alkaloid, subject to changes under chemical treatment or by keeping, these changes being in the nature of conversion into other alkaloids of a lower degree of the same poisonous power, some of them being practically inert. These weaker aconite alkaloids make up a variable part of the total alkaloid of the drug and its liquid preparations, and a still larger part of many lots of so-called aconitin alkaloid on the market. The liquid preparations of the drug, chiefly of the root, are more widely used and more relied upon in medicine than is the separate alkaloid, the latter having an uncertain place in national pharmacopeias. The total alkaloidal content of the good root is said to average from 0.75 to 1 per cent. (the pharmacopeial standard demanding not less than 0.5 per cent. of the ether-soluble alkaloids of aconite). The percentage of absolute aconitin in the root cannot well be declared from the results of analysis, but from data of physiologic effects it would appear that the poisonous power of aconite root is equivalent to not more than 0.01 to 0.02 per cent. of absolute aconitin. Wright obtained 0.03 per cent. and Juergens 0.02 per cent. of pure aconitin, besides alkaloids of lower power, from the root by analysis.

According to the U. S. Pharmacopœia, ninth revision, 100 c.c. of tincture of aconite yield not less than 0.045 nor more than 0.055 gram of ether-soluble alkaloids. Extract of aconite yields not less than 1.8 per cent. nor more than 2.2 per cent. of the ether-soluble alkaloids, while 100 c.c. of the fluidextract of aconite yield not less than 0.45 nor more than 0.55 gram of the ether-soluble alkaloids.

Aconitin proper is crystallizable, forming when crystallized from alcohol colorless rhombic prisms or plates. Indeed, it is somewhat loosely termed the crystallizable alkaloid of aconite, in contradistinction to the amorphous aconite alkaloids, which have little poisonous effect. In taste the bitterness of aconite is due to its alkaloids of less poisonous effect. Certain inert aconite products are very bitter.

Symptoms of Poisoning by Aconite.—In medicinal overdoses there are diminished force and frequency of pulse, coldness and moisture of the surface, tingling and numbness about the mouth, face, and throat, the urine being occasionally increased, although usually retained. In decidedly poisonous doses there are tingling and numb-

¹ See Geiger and Hesse, *Ann. der Chem. und Pharm.*, 1883, vii, 276; Dunstan and Ince, *Jour. Chem. Soc.*, 1891, lix, 271; Dunstan and Unmeyer, *Ibid.*, 1892, lxi, 385, 395; Dunstan and Jowett, *Ibid.*, 1893, lxiii, 443; Dunstan and Carr, *Ibid.*, pp. 491, 991, 994; Freund and Beck, *Ber. d. d. chem. Gesellsch.*, 1894, xxvii, 433, 720; Freund, *Ibid.*, 1895, xxviii, 192, 2537; Dunstan and Henry, *Jour. Chem. Soc.*, 1905, lxxxvii, 1650.

ness in the mouth, burning in the throat and stomach, flow of saliva, nausea, usually followed by marked retching and vomiting, rarely purging, grinding of the teeth, numbness and tingling of the fingers and other parts of the body, pain in the eyes and head, and difficulty in swallowing and sometimes in speaking. Cramps in the extremities, tetanic manifestations, and occasionally marked convulsions may be



FIG. 43.—Monkshood or aconite (*Aconitum napellus*).

noted. The pulse from the first is slow, feeble, and irregular, the surface cold and moist, the face bloodless, and the strength prostrated. Delirium is unusual, and stupor rarely appears as an effect of this poison.¹ Respiration is shallow, dyspneic, and rapid, but becomes slow as the case progresses. The state of the pupils varies in different stages and cases, dilatation being usually observed as the respiratory failure increases. In cases running a rapid course the symptoms are sometimes those of general shock.

Period When Fatal.

—The symptoms come on very soon—almost as soon as the poison reaches the circulation. The course is rapid. Death generally takes place in three or four hours. In one series of 6 fatal cases reported by Mallet in 1883 the shortest fatal period was eight minutes and the longest was four days.

Fatal Quantity.—Pure aconitin is one of the two or three most powerful known poisons: It is stated (see Case 3) that $\frac{1}{16}$ grain (0.004 gm.) has caused death, and that one-half of this might prove fatal. In McNally's case (see Case 10) the lethal dose was shown to be $\frac{1}{10}$ grain of the alkaloid. Ipsen gives 3 mg. ($\frac{1}{25}$ gr.) as the lethal dose, and reports recovery of the alkaloid after burial of two months.²

¹ See Baker, Brit. Med. Jour., 1882, ii, 1039; Topham, Lancet, 1851, ii, 56; Tuttle, Boston Med. and Surg. Jour., 1891, cxxv, 678; Robinson, Ibid., 1892, cxxvii, 192.

² Vrtljschr. f. gerichtl. Med., 1914, 3 f., xlvii, 1 Suppl., 180.

Experiments indicate that $\frac{1}{32}$ grain (0.002 gm.) is about the least fatal dose for man. Cases of poisoning by absorption of aconite from the surface of the body are not uncommon. Large doses of the alkaloid itself have been recovered from, but in these cases it cannot be ascertained what proportions of the alkaloid taken were absolute unchanged aconitin. The U. S. Pharmacopœia gives the minimum lethal dose of the fluidextract of aconite as 0.00004 c.c. for each gram body weight of a guinea-pig; while that of the tincture is 0.0004 c.c. per gram of body weight.

Treatment.—This consists of the evacuation of the stomach by the siphon-tube or stomach-pump, preceded and accompanied by tannic acid or finely powdered charcoal to diminish the solubility of the alkaloid. Then the remedies known as heart stimulants—ammonia, alcoholic drinks, and with observant care, the hypodermic administration of digitalis and perhaps strychnin—are indicated. The patient should be kept warm (see Cases 2, 4, 5).

Statistics.—The majority of cases of aconitin poisoning noted in the literature are accidental, 159 out of 195 by aconite and its preparations, and 19 out of 26 by aconitin; 27 cases of suicide from aconite are noted and 16 authentic cases of homicide are found in the literature.

CASES OF POISONING BY ACONITE AND ACONITIN

CASE 1.—One ounce (28 gm.) of aconite was taken by a woman forty-eight years of age. There was general collapse, the extremities were cold and clammy, and the breathing was labored and slow. The stomach was washed out and ether given hypodermically. The patient died in sixty-five minutes.¹

CASE 2.—A dram (3.5 c.c.) of Fleming's tincture of aconite, which should have been equivalent to 306 grains (20 gm.) of aconite root, was taken by a man fifty years of age. The surface of the body was cold and moist, the pulse 96, and the pupils were slightly dilated. There was vomiting. Digitalis was given hypodermically, with alcoholic drinks, followed by calomel. The patient recovered.²

CASE 3.—Of crystallized aconitin nitrate (Petit's) $\frac{1}{16}$ grain (0.0004 gm.) was taken by a feeble man sixty-one years of age, who immediately suffered from burning and constriction of the mouth extending to the stomach, and a sense of coldness of the body. The patient took repeated doses within two days, amounting in all to about $\frac{1}{2}$ grain (0.0092 gm.) of the same aconitin nitrate, and suffered from violent symptoms of aconite poisoning, so that at one time it was believed that he would die; nevertheless he recovered. From the same solution of the alkaloid the physician who had prescribed it in the case just stated himself took about $\frac{1}{16}$ grain (0.004 gm.) of the aconitin nitrate. Symptoms of poisoning appeared at the end of fifteen minutes. There were burning in the mouth, extending to the abdomen, pallor, feebleness of the extremities, a small and irregular pulse, the pupils being at first contracted and then suddenly dilated. Vomiting was induced, and ether given hypodermically. Later there were convulsions, with labored respiration. The heart failed and the patient died five hours after taking the poison.³

CASE 4.—Four teaspoonfuls of tincture of aconite were taken by a man sixty years of age. Tingling in the face, facial muscles drawn, intense coldness, weak pulse, heavy breathing, and blindness followed. Under treatment with emetics, tincture of digitalis, wine, brandy, and strychnin the patient recovered.⁴

CASE 5.—A large amount of aconite was taken by a woman thirty-six years of age who had previously taken a large amount of alcoholic liquor. The symptoms

¹ S. McWhannell, Brit. Med. Jour., 1890, ii, 791.

² McWhannell, Ibid.

³ A. Busscher, Berlin. klin. Wochenschr., 1880, xvii, 337, 356; Ann. d'Hyg., 1882, vi, p. 87; P. C. Plugge, Arch. d. Pharm., 1882, cexx, 20; Wormley's Micro-Chemistry of Poisons, 1885, 620.

⁴ M. A. Warriner, Med. Record, 1891, xxxix, 521.

were very much delayed. Treated hypodermically with digitalis, the patient recovered.¹

CASE 6.—In a case of poisoning by $1\frac{1}{2}$ ounces (45 c.c.) of Fleming's tincture of aconite, with numbness, profuse sweating, dilated pupils, general convulsions, and finally coma, treatment by emetics, brandy, digitalis, ether, and caffeine was instituted and the patient recovered.²

CASE 7.—In 1883 Mallet readily detected aconitin in the contents of the stomach of 3 out of 6 cases of fatal poisoning by aconite at the Western Asylum for the Insane in Virginia. In some manner the poison had been introduced into the medicine of 8 patients, 2 of whom recovered. Aconitin was found in the residues of the medicine taken.³

CASE 8.—In 1882 an American physician, George Henry Lamson, then resident in England, was convicted of the murder of his brother-in-law, Percy Malcolm John, by administration of aconitin. Lamson purchased 2 grains of aconitin, giving an unknown amount to John. Symptoms appeared in fifteen minutes, the subject complaining of heartburn. Violent vomiting soon appeared, accompanied by pains in the stomach, sense of constriction in the throat and inability to swallow. Great restlessness was noted, delirium being evident a few minutes before death, which occurred about three and three-quarter hours after the capsule was taken. The postmortem appearances consisted of redness of greater curvature and posterior portion of stomach; congestion of the other viscera and brain.⁴

CASE 9.—A man died suddenly from poisoning by aconite or aconitin administered, presumably, by his wife and a farm hand. Suspicion being aroused, the body was exhumed three hundred and twenty-three days after burial. In this case the dose must have been enormous, as $\frac{1}{3}$ grain (4.8 mg.) of aconitin was separated and actually weighed. The identification of the alkaloid seems to have been very conclusive, the following results being reported. Bitter taste and tingling of tongue were marked. The melting-point of the alkaloid was 186.8°C . The benzoyl radical was demonstrated. The crystalline chloraurate melted at 136°C . and showed 19.86 per cent. gold. The same writer also reports 4 other cases of aconite poisoning, one of which was buried three hundred and eighty-five days before the examinations were conducted.⁵

CASE 10.—A man (N. A.), aged thirty-eight, was given a prescription calling for 1 grain of aconitin in 20 capsules, with directions to take one every three hours. One capsule was taken at 7.30 p. m., one hour after which the patient complained of prickling sensations in arms, body and lower extremities, with an increasing weakness. At 10.30 p. m. a second capsule was given. Five hours thereafter the patient complained of faintness and tingling sensations; body was covered with a cold sweat; respiration slow and irregular; no convulsions; no vomiting or diarrhea; pupils dilated. Patient was very restless, became unconscious and died five hours and twenty minutes after taking the second capsule, that is, after taking $\frac{1}{10}$ grain of aconitin. Postmortem examinations showed the lungs markedly edematous and engorged with blood; heart showed general excentric hypertrophy; marked arteriosclerosis; acute parenchymatous degeneration of myocardium; kidneys and liver revealed passive hyperemia and marked parenchymatous degeneration; gastrointestinal tract no gross changes. Chemical examination of stomach gave a non-crystalline alkaloid of bitter taste and productive of tingling sensation of the tongue. Alkaloid was precipitated from solution by Wagner's, Mayer's, and Sonnenschein's reagents. Amorphous precipitate with gold chlorid. Cardiographic tracing of heart of frog weighing 30 grams, poisoned with $\frac{1}{10}$ grain of the alkaloid, showed at first a quickening of the beat, later beats slow and irregular, with final arrest in diastole in one hour. Residue obtained from kidney had a slightly bitter taste and produced a tingling sensation on the tongue. Residues from liver and intestines were inert.⁶

CASE 11.—Subject ate freely of meat with "horse-radish" sauce, made by mis-

¹ C. F. Dereum, *Med. and Surg. Reporter*, 1889, lxi, 376.

² C. C. Bradley, *Med. Record*, 1887, xxxii, 155.

³ *Pharm. Jour. and Trans.*, 1883, 3 S., xiii, 901.

⁴ *Reg. v. Lamson*, Central Criminal Court, Sessions Paper, xcv, pt. 569, pp. 547-590; *Stevenson*, *Guy's Hosp. Rep.*, 1883, 3 s., xxvi, 307; *Dupré*, *Lancet*, 1882, i, 455; *Westm. Hosp. Rep.*, 1885, i, 105; *Review of Lamson Case*, *Brit. Med. Jour.*, 1913, ii, 1306.

⁵ *Carel*, *St. Paul Med. Jour.*, 1906, viii, 666.

⁶ *McNally*, personal report (March 1, 1917) from office of Coroner's Chemist, Chicago, Ill.

take from aconite root. Fifteen minutes after dinner experienced tingling all over body and felt giddy and restless. Skin cold and clammy; pupils equal and medium, but later widely dilated; heart irregular, with pulse of 70; no vomiting; respiration shallow and barely perceptible; twitching of left shoulder and facial muscles. Under treatment with apomorphin, digitalin, and strychnin patient recovered. Examination of sauce showed presence of aconitin.¹

Postmortem Appearances.—These are not markedly characteristic. The lungs, liver, kidneys, and brain are generally found somewhat congested. Effusions may be observed in the pericardium and in the ventricles of the brain. The stomach is sometimes reddened. The blood is found abnormally fluid, and sometimes of a bright red color.

Tests for Aconitin.—In cases of poisoning by the liquid preparations of aconite the poisonous alkaloid itself is the only aconite constituent capable of being recovered and identified in analysis. As already stated, aconitin is an unstable alkaloid, a fact that adds to other difficulties in its recovery and identification. It reacts weakly alkaline to litmus; is readily soluble in chloroform and benzene (1 part in 7), less easily in alcohol (1 in 28), and ether (1 in 65), very slightly in water, and almost insoluble in petroleum ether; it is dextrorotatory, while its salts are levorotatory. When heated rapidly it melts at about 195° C. (383° F.), giving off acid vapors, various specimens of the alkaloid differing in the melting-point. The alkaloid readily undergoes hydrolysis or saponification, even by boiling with water, yielding benzoic and acetic acids, and finally the inert amorphous base aconin ($C_{25}H_{41}NO_9$). This aconin is dextrorotatory; is easily soluble in water and alcohol, and is bitter in taste, but does not produce numbing and tingling of the tongue.

The identification of aconitin in toxicology rests upon physiologic effects, and less clearly upon chemical reactions, as follows:

Biologic Tests.—1. **Tingling of the Lip.**—When an aqueous solution of the free alkaloid or one of its salts is applied to the lip or tongue a bitter taste is noted, followed by numbness and tingling, the effect passing away very slowly. A single drop of a 1 : 100,000 aqueous solution may be applied. If the solution be so strong as to cause burning, it should be diluted, and care should be exercised to avoid taking an injurious dose. According to Squibb,² the alkaloids of $\frac{3}{10}$ grain (0.02 gm.) of good aconite root, in solution made up to 1 fluidram (4 c.c.), held in the anterior part of the mouth, previously rinsed with water for sixty seconds and then ejected, give a tingling sensation, beginning in five or ten minutes and lasting about one and one-half hours, as an average effect upon different persons. When the soluble part of only $\frac{1}{10}$ grain (0.006 gm.) of the root was taken, the tingling

¹ Livingston, Brit. Med. Jour., 1915, i, 928. For other cases of aconite or aconitin poisoning see Magill (Condon case), Medical News, 1902, lxxx, 1019; Fellitar, Pest. med. chir. Presse, 1904, xl, 603; Seba, Med. Herald, 1909, xxviii, 355; Maurel, Compt. rend. soc. de biol., Paris, 1909, lxxvii, 477; Bhagat, Pract. Med., 1910, viii, 205; Edgcombe, Lancet, 1910, ii, 1270; Inglis, Ibid., 1911, i, 162; Garnier, Ann. d'hyg., 1916, 4 s., xxv, 97.

² Ephemeris, 1882, i, 125.

effect began after fifteen minutes and lasted for from one-quarter to one-half hour.

2. **Upon an Animal.** The final solution, prepared as for Test 1, is given hypodermically to a mouse or injected into the lymph-sac of a frog. The death of the animal, usually within an hour, gives evidence of the poison. A cardiographic tracing of the heart's action shows a tetanization of the heart muscle followed by a peculiar wave-like action and final arrest in diastole.¹

Chemical Tests.—1. The general reagents for alkaloids, as stated on page 421, give precipitates with aconitin. Auric chlorid gives a yellow, amorphous precipitate that can be crystallized from alcohol. This gold salt ($C_{34}H_{47}NO_{11}HCl.AuCl_3$) crystallizes with 3 molecules of water or without water in needles or rectangular prisms. The former melts at $136^\circ C.$ ($276.8^\circ F.$) and contains 19 per cent. of gold; while the latter (the anhydrous salt) melts at $145^\circ C.$ ($293^\circ F.$) and contains 20 per cent. of gold.

2. A small portion of the solid residue, obtained in the extraction process, dissolves in concentrated sulphuric or nitric acid without color or, at most, with a slight yellow coloration. If a portion of this solid residue be treated with 2 or 3 drops of concentrated sulphuric acid containing 5 mg. of ammonium vanadate per cubic centimeter, an orange color is produced in the presence of aconitin. If a portion of the solid residue be warmed with a few drops of sulphuric acid and a small crystal of resorcin be added while still warming, an orange (yellowish-red) color is produced.

3. **Alvarez's Reaction.**—Place a portion of the purified solid residue, obtained in the extraction process, in a small porcelain dish and add 5 to 10 drops of pure bromin. Heat on the water-bath, add 1 to 2 c.c. of strong nitric acid, and evaporate to dryness again, adding a few drops more of bromin if the nitric acid loses its color. To the yellow oxidation product thus formed add $\frac{1}{2}$ to 1 c.c. of a saturated alcoholic sodium hydrate solution and again evaporate to dryness. A red or brown residue is obtained depending on the amount of aconitin present. Allow to cool and add 5 to 6 drops of a 10 per cent. aqueous solution of copper sulphate, when a beautiful deep green color is observed if aconitin be present. This reaction is given with the pure aconitin containing only a slight amount of amorphous basic impurity, a distinct green being obtained with 0.1 mg. of aconitin. None of the better known alkaloids were found by Alvarez to give this reaction.²

4. **Palet's Reaction.**—Place a portion of the purified solid residue in a small porcelain dish and add a few drops of a mixture consisting of 25 grams of concentrated ("syrupy," 85 per cent.) phosphoric acid and 1 gram of sodium molybdate. Heat directly over a small flame until vapors appear, when a very brilliant violet color is formed in the presence of aconitin. This reaction is said to differentiate aconitin from

¹ See Fühner's monograph, *Nachweis und Bestimmung von Giften auf biologischem Wege*, 1911, 102; also Fühner, *Arch. f. exper. Path. u. Pharm.*, 1911, lxxvi, 179.

² *Chem. News*, 1905, xci, 179.

apomorphin, atropin, brucin, caffen, cocain, codein, digitoxin, digitonin, emetin, morphin, napellin, narcein, narcotin, papaverin, strychnin, and theobromin. Only aspidospermin and veratrin give similar colors, which differ, however, from the aconitin test, the former by the action toward oxidizing substances, the latter toward mineral acids.¹

5. Moisten the residue with nitric acid, evaporate to dryness, cool, and add a drop or two of alcoholic solution of caustic potash to obtain the odor of ethyl benzoate. This test is not applicable to quantities as small as those usually in question in toxicology.

Pharmacognosic Test.—If poisoning by aconite as a crude drug or fresh plant be in question at all, the contents of the stomach should be inspected for fragments of roots, leaves, or bark, and these subjected to a botanical examination. A microscopic examination for the powder of the root may be made upon the collected and washed residue of the contents of the stomach.

Separation of Aconitin from the Tissues.—This is to be undertaken with precautions against hydrolysis of the alkaloid. The process elsewhere directed for atropin is to be employed, extracting with alcohol, preferably at room temperature for a time and then at a temperature not above 60° C. (140° F.). After separating the fat by allowing the extracts to stand in the ice-box, the fat is removed and the filtrate is evaporated at a low temperature under a vacuum. Both ether and chloroform should be used as immiscible solvents.

Deposition in the Body.—Beside the stomach, the urine, the kidneys, and the liver are to be examined. Aconitin is excreted, especially in the urine and the saliva (Kobert). Although Basot² and Vibert³ state that aconitin is one of the alkaloids which is non-resistant to putrefactive processes, Lewin⁴ asserts that it is not altered under conditions of decay. Recently Palet⁵ has shown, by experiments on white rats injected subcutaneously with lethal doses of aconitin and buried in metallic boxes, that the alkaloid could be readily detected after a lapse of two months. In the analysis of the viscera of Gabriela de la Asuncion Correa, Palet⁶ isolated a putrefactive product which showed some of the reactions of aconitin, but differed in certain respects, especially in its lack of toxic properties and in the identity of the color reactions obtained. This case emphasizes the necessity for insistence upon absolute similarity of the color reactions of a residue with those obtained with known samples of the suspected alkaloid.

Failure to Detect.—The conclusion of Haines⁷ is certainly just when he says: "If a small but fatal dose of the poison were to be given, especially if it were administered hypodermically, the chances of its detection in the body after death would not be great."

¹ Jour. pharm. chim., 1919, xix, 295; Ann. Soc. Quim. Argentina, 1919, vi, 28, 483; see also Mallanneh, Analyst, 1921, 46, 193, for further reaction.

² Thèse de Paris, 1889, p. 50.

³ Précis de Toxicologie, Paris, 1915, p. 695.

⁴ Lehrbuch der Toxikologie, 1903, p. 570.

⁵ Santana, Med., 1919, xxvi, 166.

⁶ Ibid., 424.

⁷ Hamilton's System of Legal Medicine, 1894, i, 423.

ATROPIN AND RELATED ALKALOIDS

General Description and Relations.—The atropin series of alkaloids embraces a number of very closely related bases, of which the most important are atropin, hyoscyamin, and scopolamin (hyoscin). They are found in various parts of several plants of the solanaceæ group (often occurring together), among which are *Atropa belladonna* (deadly nightshade), *Datura stramonium* (thorn-apple, Jamestown or jimson weed), *Hyoscyamus niger* (henbane), *Duboisia myoporoides* and *Mandragora officinale* (mandrake). While other alkaloids, such as duboisin,



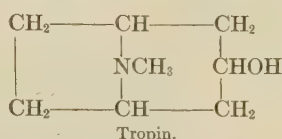
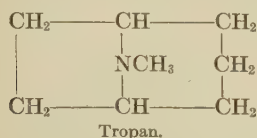
FIG. 44.—Belladonna, or deadly nightshade (*Atropa belladonna*).

mandragorin, and daturin have been described, these are, unquestionably, simply mixtures of the chief alkaloids above mentioned and are not true chemical entities. However, certain basic substances, such as atropamin (apoaotropin), belladonnin, and bellatropin, are occasionally found in these solanaceæ, but do not possess any special toxicologic value.¹

As shown by saponification of the above alkaloids on heating with water, acids or strong alkalies, all of the atropin series of alkaloids, with exception of scopolamin, are ester-like combinations of an aromatic

¹ See Schmidt, Pflanzenalkaloide, in Biochemisches Handlexikon, 1911, v, 90.

acid with a base¹ known as tropin ($C_8H_{15}NO$). Such acid esters of tropin are known as tropeins. Tropin belongs to the tropan-ring² system of alkaloids, which consists of a peculiar combination of a 6 atomic group (pyrrolidin) with a 5 atomic group (piperidin) forming a complex derivative with a peripheral 7 carbon atomic ring, thus:



Tropin is optically inactive and crystallizes from absolute ether in large plates, which melt at $63^\circ C.$ ($145.4^\circ F.$). It is very readily soluble in water and alcohol. Owing to the optical inactivity of the base, the difference in rotatory power of atropin and hyoscyamin, which are isomeric, must be due to the acid in combination in these tropeins. While the chemistry of these bodies is of more than passing interest, it is of importance in toxicologic work only in so far as it bears on the properties of the alkaloids and their possible conversion, the one into the other.

Symptoms of Poisoning by Atropin and its Related Alkaloids.—Poisoning by belladonna, hyoscyamus, stramonium, and *Duboisia myoporoides* is due to the alkaloids of the atropin family, and is attended by the same leading symptoms—marked dryness of the mouth and throat, due to paralysis of terminations of chorda tympani nerve leading to diminution of saliva; redness of the tongue; huskiness of the voice; thirst; difficulty in swallowing; wide dilatation of the pupils, a few cases being, however, reported in which there was no dilatation³; eyes prominent, brilliant, wild and staring; impaired vision and loss of all accommodation of the eye; hallucinations; giddiness and vertigo; then well-marked delirium; excitement, which may be silent and muttering but is usually violent, the patient becoming belligerent although he may, occasionally, be simply hilarious; and sometimes chorea-like movements or convulsions. Nausea is common and vomiting is not unusual. Urine is usually retained, but may, at times, be freely voided.⁴ Atropin is eliminated principally by the urine,⁵ while hyoscyamin seems not to be eliminated by the urine or, at least, not to any extent.⁶ The pulse is at first full and bounding, but becomes feeble and rapid, and sometimes intermittent and even imperceptible, due to paralysis of the terminations of the vagus in the cardiac musculature. Respiration becomes quicker and deeper, frequently interrupted by convulsive movements of the respiratory muscles, that is the respira-

¹ See Ladenburg, Ber. d. d. chem. Gesellsch., 1879, xii, 941; 1880, xiii, 104; Ann. der Chemie, 1883, ccxvii, 74.

² See Willstätter, Ber. d. d. chem. Gesellsch., 1895, xxviii, 3273; 1897, xxx, 2692; 1898, xxxi, 1535, 2498, 2660; Ann. der Chemie, 1901, cccxvii, 307, 315.

³ See Ghose, Indian Lancet, 1905, xxv, 125; also McNally, Jour. Amer. Med. Assoc., 1915, lxv, 1640.

⁴ See Stalberg, Amer. Jour. Med. Sci., 1904, cxxvii, 517.

⁵ See Ipsen, Vrtljschr. f. ger. Med., 1906, xxxi, 308.

⁶ See Couto-Jardin, C. R. Acad. Sc., 1902, liv, 1054.

tion is at first stimulated but later is markedly depressed. Skin is dry and hot, although it may become cool soon after the symptoms are established. A deep red eruption upon the skin has been observed in many cases. In the later stages numbness and paralysis of the limbs sometimes occur, and before death there is generally coma, and occasionally there are convulsions. After recovery the patient usually has no memory of what has transpired.¹ The temperature may be subnormal, but is often much above normal (see Case 24).

The dilatation of the pupil is due to local action, atropin paralyzing the myoneural junction (termination of the motor oculi nerve) in the circular muscle of the iris. Introduced into the circulation at large, the poison affects both eyes; applied externally to one eye, its pupil



FIG. 45.—Stramonium (*Datura stramonium*).

only is dilated. The pupil is dilated to some extent in some stages of the action of cocain, and sometimes under the action of digitalis and of coniin, but these effects do not simulate the extent and persistent dilatation of atropin poisoning.

The effects of hyoscyamin are practically the same as those of atropin, differing only in degree, as the former is rarely pure being changed as stated below into atropin when in solution. The narcotic influences attributed to hyoscyamin are due to the presence of scopolamin as an impurity and not to the hyoscyamin itself. Hyoscyamin acts almost twice as strongly as atropin on the peripheral nervous end-organs, while its influence on the central nervous system is the same.

¹ See, however, Jepson, West Virg. Med. Jour., 1907, ii, 201.

This is explained by Cushny, as follows: "The action of atropin, as has been stated, is compounded of that of natural or levorotatory hyoscyamin with that of its dextrorotatory isomer. The latter does not exist free in nature and possesses only a feeble action on the nerve terminations, while it stimulates the spinal cord of the frog more than either atropin or hyoscyamin. The peripheral action of atropin is thus due to its containing hyoscyamin, and as a grain of atropin con-



FIG. 46.—Henbane (*Hyoscyamus niger*).

tains only $\frac{1}{2}$ grain of hyoscyamin, the former naturally exercises only half the effect of 1 grain of hyoscyamin. On the other hand, the $\frac{1}{2}$ grain of dextrorotatory hyoscyamin in 1 grain of atropin is almost inert on the nerve terminations, but exercised the same effect on the central nervous system as its levorotatory complement. Atropin thus acts on the central nervous system in mammals in the same strength as hyoscyamin, but only half as strongly in the periphery." Although hyoscyamin shows a stronger action in some respects than does atropin,

the larger dose of the similar pharmacopeial preparations of hyoscyamus, as compared with those of belladonna, is attributable to the lesser alkaloidal content of the former. Thus, *Fluidextractum hyoscyami* yields not less than 0.055 per cent. nor more than 0.075 per cent. of the alkaloids of hyoscyamus; while *Fluidextractum belladonnæ radices* yields not less than 0.405 nor more than 0.495 per cent. of the alkaloids of belladonna.¹

The effects of scopolamin correspond to those of atropin, except that it depresses the central nervous system more markedly than does atropin, while its peripheral action is about the same as that of hyoscyamin. Scopolamin poisoning shows its greatest variation from that of the other tropeins in the usual nervous symptoms observed. Thus, there is a marked sensation of fatigue and drowsiness; patient becomes quiet, moves and speaks less, and soon falls asleep. In some cases, however, the stage of excitement noted with atropin may precede the sleep, especially after large doses when the symptoms may be indistinguishable from those due to atropin. It does not seem to be as dangerous as the other members of this group, while a certain degree of tolerance may be acquired by its use. This drug is used in combination with morphin in production of so-called "twilight sleep." This association has caused many toxic effects, although few deaths are reported.

Homatropin, an artificial tropein, is much milder in its poisonous effects. The dilatation of the pupil, although equally decided, appears earlier and passes away much sooner than that of the natural tropeins. This drug is used only for its action on the eye, yet 20 cases of non-fatal poisoning have been reported following its employment.²

Among the products of putrefaction of animal tissue, such as decomposing fish, canned beef, putrid game, and sausage, there may not infrequently be found substances, the so-called "**ptomatropins**," which, in their mydriatic properties, resemble atropin and hyoscyamin and which more than once have figured in medicolegal cases. The symptoms, following their intake into the system, often closely resemble those of belladonna poisoning. While these putrefactive basic substances resemble, both as to symptoms produced and chemical reactions observed, the atropin group of alkaloids, yet the careful analyst will not be misled by these substances as his methods should exclude their presence in his purified residue or, if not, his final tests will show considerable variance in many of his reactions. It is important, in this connection, to remind the analyst that single reactions should never be made the basis of an unequivocal report as to the identity of a residue.

Period When Fatal.—The symptoms of poisoning by atropin and its related alkaloids appear within a few minutes after absorption of the drugs into the blood, and usually, although not invariably, within an hour after the drugs or the alkaloids have been taken into the stomach. The usual course of the poisoning is not rapid, and in a probable

¹ See Cushny, Jour. Pharmacol., 1921, 17, 41, for comparative effects of the optical isomers.

² See Clay, Hahnemannian Monthly, 1920, iv, 690.

majority of fatal cases death has occurred within twenty-four hours from the time when the poison was taken.

Fatal Quantity.—Constitutional differences are so great in the power to recover from atropin poisoning that any statement as to the smallest fatal dose is liable to be misleading. Recovery occurs in a majority of the cases. According to the statistics of Falck, quoted by Kobert,¹ recovery was the result in 88.4 per cent. of the cases collected. The smallest quantity of atropin known to have caused death, in so far as the literature reveals, is the case reported by Burrenrich² of the installation of 0.0004 gram (0.006 gr.) into the eye of a four year old child. Arnold³ reports a death from the hypodermic administration of $\frac{1}{30}$ grain of atropin; Fabris⁴ cites a case of death from $\frac{1}{20}$ grain; Dunlap⁵ relates the death of a patient in forty-one hours from $\frac{1}{16}$ grain, and Jaenicke⁶ records the death of a woman from $\frac{1}{13}$ to $\frac{1}{16}$ grain of atropin sulphate. While such small quantities have proven fatal, much larger doses have been recovered from; thus, Macchiavelli⁷ reports recovery following intake of 7.7 grains of atropin sulphate with suicidal intent. External application of atropin or of preparations of belladonna or hyoscyamus may produce toxic results.⁸ Although the usual fatal dose of the berries of *Atropa belladonna* is stated as from 3 to 10 berries, Kanngiesser⁹ himself ate, for experimental purposes, 10 berries and recovered.

It is a difficult matter to give a definite statement concerning the lethal dose of stramonium (datura), as extremely large doses have been recovered from while smaller doses have proved fatal. Thus, Williams¹⁰ reports recovery from the effects of taking 71 c.c. of the tincture of stramonium, containing about $\frac{1}{10}$ grain of alkaloids; while McNally¹¹ records the extraction of 2.2 mg. ($\frac{1}{30}$ gr.) of alkaloid from the stomach contents of a child dead from the effects of eating stramonium seeds. In this case, however, the amount isolated represents, of course, only a fraction of the amount taken, so that the fatal dose was undetermined. The number of seeds of thorn-apple necessary to produce death varies remarkably. Thus, a child of two and a half years died from eating 16 grains of the seeds,¹² while in McNally's case, above cited, the boy ate about 180 seeds; on the other hand, a girl aged eight recovered after swallowing 237 of these seeds.¹³

¹ Intoxikationen, 1906, ii, 1043.

² Ann. et bull. Soc. méd. de Gand, 1891, p. 288.

³ Baltimore Med. Jour., 1871, p. 169.

⁴ Quoted by Modica, Gazz. d. osp., 1898, xix, 683.

⁵ Amer. Pract. and News, 1887, iii, 230.

⁶ Deutsch. Arch. f. klin. Med., 1877, xx, 617.

⁷ Gazz. med. ital. lomb., 1880, ii, 339; see also Meyer, Corr.-Bl. f. Schweiz. Aerzte, 1905, xxxv, 548.

⁸ Nathan, Brit. Med. Jour., 1914, i, 965.

⁹ Münch. med. Wehnschr., 1911, lviii, 2505; see also Kratter, Vrtljschr. f. ger. Med., 1886, xlv, 73.

¹⁰ New England Jour. Med. and Surg., 1823, xii, 253.

¹¹ Jour. Amer. Med. Assoc., 1915, lxx, 1640.

¹² Duffin, London Med. Gaz., 1834, xv, 194.

¹³ Friedman, Jahrb. f. Kinderh., 1891, xxviii, 354.

Concerning the lethal dose of hyoscyamus, hyoscyamin, homatropin, and scopolamin little is known. No fatal cases of poisoning with homatropin have been reported. According to Kobert,¹ 12 fatal cases of scopolamin poisoning resulted from the use of this drug in 1200 cases of anesthesia. The smallest fatal dose of scopolamin reported is that of Ely,² in which death followed the administration of $\frac{1}{8}$ grain of morphin with $\frac{1}{100}$ grain of scopolamin hydrobromid. Recovery has followed from a dose of 7 mg. ($\frac{1}{10}$ gr.) as reported by Zimmermann,³ while Korn⁴ and Stolle⁵ record recovery from doses of 0.01 gram (about $\frac{1}{4}$ gr.), and 0.015 gram (about $\frac{1}{5}$ gr.) respectively.

Treatment.—The aim is—(1) To remove the contents of the stomach and wash out the organ; (2) to improve any possibility of precipitation of any unabsorbed portion of the alkaloid; (3) to combat carefully the absorbed alkaloid by the physiologic effects of morphin, possibly of pilocarpin.

1. For the first indication use a siphon-tube and water at ordinary temperature; this is more effective than emetics.

2. If it be undertaken to precipitate any of the alkaloid in solution in the stomach before the evacuation of this organ, administer 6 minims of compound solution of iodine diluted with water (3 or 4 ounces). The weight of the free iodine should be as much as four times the weight of the atropin to be precipitated. The stomach should be washed out without delay after the iodine is given. Instead of the iodine, an excess of tannic acid may be employed (see Case 9). The administration of finely powdered charcoal is a resource, instead of either of the precipitants just named, to hold the alkaloid for a short time and retard its absorption.

3. To oppose the poison by the physiologic effects of morphin the latter is administered hypodermically in full medicinal doses, repeated as indicated by their effects upon the eye, the pulse, and the respiration (see under Morphin, p. 518, and under Atropin, Cases 8, 11, 25). It must be recalled that morphin depresses the respiration, so that its use may be dangerous in cases in which the depressant effects of atropin have become manifest. In this depressant stage, caffeine may be used and artificial respiration vigorously employed. Pilocarpin was administered in Cases 20 and 21 (this may prove of little avail, especially in antagonizing the effects of atropin on the central nervous system); physostigmin in Cases 10 and 19; potassium bromid and chloral in Case 25. Chloroform and ether may be used to control the excited condition and violent delirium, but should be stopped when these symptoms pass off.

Statistics.—The large majority of cases of poisoning with the atropin series of alkaloids is accidental, suicidal, and homicidal cases being relatively rare. Thus, of 383 cases of belladonna poisoning, 303 were accidental, 9 suicidal, 6 homicidal, and 65 of uncertain origin;

¹ Intoxikationen, 1906, ii, 1054.

² New York Med. Jour., 1906, lxxxiv, 799.

³ Münch. med. Wehnschr., 1912, lix, 423.

⁴ Therap. Monatsh., 1891, v, 648.

⁵ Allg. Ztschr. f. Psychiat., 1900, lvii, 151.

of 317 cases of atropin poisoning, *per se*, 252 were accidental, 29 suicidal, 8 homicidal, and 28 uncertain; of 273 cases of stramonium poisoning, 176 were accidental, 3 suicidal, 12 homicidal, and 72 uncertain. Recovery was the rule in these cases, of the 973 above mentioned, 92, or about $9\frac{1}{2}$ per cent., were fatal.

CASES OF POISONING BY THE TROPEIN ALKALOIDS OR BY DRUGS CONTAINING THEM
By Atropin:

CASE 1.—A woman fifty-nine years of age took 1 grain (0.065 gm.) of atropin sulphate. The symptoms that followed were glassy eyes and dilated pupils, delirium, great thirst, numbness of hands and feet, the surface of the entire body being a scarlet red, pulse 100, temperature 101° F., and frequent urination. Recovery.¹

CASE 2.—A man of thirty-six years was treated with $\frac{1}{16}$ grain (0.004 gm.) of atropin hypodermically. Dryness of mouth and throat, dimness of sight with dilated pupils, full, strong pulse (76), breathing quiet and regular. Recovery.²

CASE 3.—A woman took $3\frac{1}{2}$ grains (0.225 gm.) of atropin sulphate. Symptoms that followed consisted of widely dilated pupils, numbness, weak pulse (70), spasms, and insensibility for nine hours. Treatment consisted of emetics and brandy and water. Recovery.³

CASE 4.—A woman of twenty-five years took about $\frac{1}{2}$ grain (0.02 gm.) of atropin sulphate. Hysterical screaming, loss of accommodation of the eyes, convulsions, very weak and slow respiration, great thirst, and profuse urination followed. Recovery.⁴

CASE 5.—A woman of twenty-six years took $\frac{3}{4}$ grain (0.05 gm.) of atropin sulphate, which was followed by furious delirium, dilated pupils, and collapse. Treatment consisted of morphin hypodermically. Recovery.⁵

CASE 6.—A boy of seven years was treated with an *external application* of a solution of atropin to relieve a burn. Delirium, great thirst, dilated pupils, dimness of vision, pulse 160, temperature 99° F., followed. Treatment by cognac and turpentine. Recovery.⁶

CASE 7.—A woman of forty years took $\frac{1}{2}$ grain (0.033 gm.) of atropin sulphate. Symptoms were dilated pupils and diminished vision, weak pulse of 116, temperature $96\frac{3}{4}^{\circ}$ F., respirations 3 a minute. Treatment by morphin and coffee. Recovery.⁷

CASE 8.—A child of two years took $\frac{1}{2}$ grain (0.022 gm.) of atropin. Symptoms consisted of dilated and immovable pupils, dry skin, scarlet rash, a pulse of 160, and restlessness. Treatment: morphin subcutaneously. Recovery.⁸

CASE 9.—A woman took $\frac{1}{2}$ grain (0.03 gm.) of atropin. Symptoms: dilated pupils, delirium, unconsciousness, pulse 100. Treatment: cognac, iodine in solution of potassium iodid, tannic acid. Recovery.⁹

CASE 10.—A man of thirty-five years received a hypodermic injection of morphin and atropin together. He became delirious and unconscious. Treatment: physostigmin hypodermically. Recovery.¹⁰

CASE 11.—A woman of twenty-seven years took a mixture of atropin and morphin. There was deep coma; the skin was cyanotic and cool; the pupils were greatly dilated; the respirations numbered 5 or 6; pulse 90; delirium and retention of urine. The patient recovered. Some of the contents of the stomach were found to contain both atropin and morphin, and both these alkaloids were also found in the urine.¹¹

CASE 12.—A man of forty-five years took at least a teaspoonful of *liquor atropiæ sulphatis* (nearly 1 per cent. strength) on August 6th, and died on August 10th. The

¹ L. Ott, Med. News, Philadelphia, 1895, lxvii, 628.

² C. Bing, Berl. klin. Wehnschr., 1895, xxxii, 997.

³ E. A. B. Traverse, Med. Jour., London, 1889, i, 1051.

⁴ G. Bentzen, Schmidt's Jahrb. d. Med., 1885, ccviii, 131.

⁵ Crozier, Amer. Jour. Med. Sci., 1875, lxi, 574.

⁶ Kjelberg, Schmidt's Jahrb. d. Med., 1881, exci, 129.

⁷ L. Eliot, Med. Record, New York, 1883, xxiv, 372.

⁸ Warfvinge, Schmidt's Jahrb. d. Med., 1885, ccv, 135.

⁹ F. Osbeck, Ibid., 1885, ccviii, 131.

¹⁰ J. Hudson, Brit. Med. and Surg. Jour., 1881, i, 918.

¹¹ F. Deutschmann, Schmidt's Jahrb. der Med., 1883, cxxvii, 234.

poison was taken at 1 p. m., and the pupils were not affected until 1.39 p. m., becoming almost fully dilated by 2.45 p. m. At autopsy the pupils were found slightly dilated; the heart enlarged and very soft; the liver and kidneys soft; the body not rigid; the abdomen swollen and tympanitic.¹

CASE 13.—A neurasthenic woman verging upon melancholia took a solution containing 3 grains of atropin. She was seen in less than twenty minutes thereafter. Pulse was very weak and rapid, reaching 160. One hour after taking the drug the axillary temperature was 105° F. Fifty minutes later it had reached 106° F., the pulse remaining the same. At this time a peculiar red rash appeared on the chest. One hour later the temperature dropped to 103.5° F. and pulse to 150. The urine, withdrawn four hours after ingestion, contained atropin. Following morning the temperature was normal, pulse 108, and respirations 24.²

CASE 14.—A man of fifty-two years drank some whisky at 3.30 on April 25th. He was seized at once with marked pains, became sick and unconscious. The doctor arrived about four hours later and sent patient to hospital, where the following findings were noted: Patient unconscious; pupils dilated and insensible to light; face deep red; no reaction to a call or to needle puncture; athetotic movements of extremities and face muscles; pulse of strong tension, regular, 140 per minute; respirations regular and deep, 17 per minute; urine retained, but was withdrawn later by catheter; temperature taken next morning showed 40.2° C. Usual treatment instituted. About 7 p. m. on evening of April 26th patient suddenly became cyanotic, pulse small and almost imperceptible, death resulting in a short time. No postmortem made. Some of the stomach contents removed with tube showed atropin, as did also the urine. Examination of fluid in the bottle from which patient drank showed atropin sulphate in a strength of 31.9 per cent.³

CASE 15.—A woman had been taking atropin for eye trouble. Suddenly manifested general symptoms of atropin poisoning. The interesting point of this case was the unusual duration of the mental symptoms, the patient showing hallucinations of a marked degree for six weeks.⁴

By Belladonna:

CASE 16.—A boy of six years ate berries of *Atropa belladonna*. Dilated pupils, delirium, unconsciousness, dryness and itching of the skin, pulse of 120 followed. Recovery.⁵

CASE 17.—A woman applied a belladonna plaster to her breast. Dimness of sight, thirst, and a rash upon the limbs followed.⁶

CASE 18.—A woman applied a belladonna plaster over the lower portion of the back. There followed dryness of the mouth, throat, and skin, hyperesthesia of the senses, symptoms peculiar to locomotor ataxia, and frequent and excessive urination.⁷

CASE 19.—A man of fifty-seven wore "a strong belladonna plaster" over his loins. There resulted dryness of the mouth and tongue, numbness of the hands and feet, dimness of sight, delirium, and a comatose condition. The skin under the plaster was very cold. Treatment: physostigmin. Recovery.⁸

CASE 20.—A woman of forty-two years took 2 ounces and 2 drams (64 c.c.) of belladonna liniment. The pupils became dilated, the face swollen, the pulse almost imperceptible, the respirations numbered 25, and there was a profound stupor. Treatment: pilocarpin hypodermically. Recovery.⁹

CASE 21.—A woman of thirty-seven years took a tablespoonful of belladonna

¹ A. S. Greenway, Brit. Med. Jour., 1878, ii, 516.

² L. L. Beehler, Jour. Amer. Med. Assoc., 1912, xxxviii, 1081.

³ Wolter, Berl. klin. Wehnschr., 1912, xlix, 1887.

⁴ Burr, Arch. Ophthal., 1913, xlii, 136. For further cases of atropin poisoning see Pouchet, Ann. d'Hyg., 1889, xxi, 139; Brouardel, Ogier et Vibert, Ibid., 1900, xliii, 9; Ipsen, Vrtljschr. f. ger. Med., 1906, xxxi, 308; Elsner, Ztschr. f. Augenhkde, 1909, xxii, 387 and 507; Franklin, Indian Med. Gaz., 1909, xlv, 20; Kucera, Klin.-Therap. Wehnschr., 1909, xvi, 345; Crespín, Provence méd., 1910, xxi, 545; Geddes, South African Med. Jour., 1913, xi, 308; Rodriquez, Rev. méd. Cubana, 1913, xxii, 131; Rathje, Ztschr. f. Veterinärk., 1915, xxvii, 1; Heubner, Deutsche. med. Wehnschr., 1919, lxxv, 758; Forsythe, Jour. Amer. Med. Assoc., 1920, lxxv, 177.

⁵ S. R. Scofield, Lancet, London, 1895, ii, 199.

⁶ Griffith, Brit. Med. Jour., 1891, i, 1060.

⁷ E. E. Maddox, Amer. Jour. Med. Sci., Philadelphia, 1893, cvi, 572.

⁸ H. J. Howarth, Lancet, London, 1894, i, 204.

⁹ N. Grattan, Lancet, London, 1881, i, 951.

liniment. The pupils became widely dilated, the breathing stertorous, and the patient entirely unconscious; the heart was weak and greatly excited, the extremities were cold. Treatment: pilocarpin and coffee hypodermically. Recovery.¹

CASE 22.—A woman of seventeen years took 2 tablespoonfuls of mixed liniments, *belladonna* and *aconite*. Symptoms: dilated pupils, pulse barely perceptible, heart-beats reaching 300, teeth clenched, violent spasms, and stertorous breathing. Death occurred in one hour and twenty minutes.²

CASE 23.—A man of thirty-three years took a mixture of more than $\frac{1}{2}$ ounce of belladonna liniment, 2 teaspoonfuls of laudanum, and a little camphorated chloroform. Symptoms: widely dilated pupils, staring eyes, violent rolling of the head, sore throat, and unconsciousness. Recovery followed without treatment.³

CASE 24.—A boy received 10 minims of tincture of belladonna three times daily for one week. At the end of this period he manifested symptoms of poisoning in which the special characteristics were marked delirium with hallucinations. On stopping the drug recovery was prompt.⁴

By *Stramonium*:

CASE 25.—A child of three years ate stramonium seeds. The symptoms that followed consisted of dilated pupils, bright red, hot and dry skin; pulse full, tetanic convulsions. Treatment: emptying the stomach, potassium bromid, chloral hydrate. Recovery.⁵

CASE 26.—A boy of three ate some "thorn apples" (*Datura stramonium*). Pupils became widely dilated; pulse 160; respiration 64; with occasional convulsions. Treatment: castor oil and morphin. Recovery.⁶

CASE 27.—A boy of seven years died suddenly. Ate seeds (about 180) of stramonium about 5 p. m. He ate supper at 6 p. m.; retired at 8 p. m. feeling well; at 12.15 a. m. complained of being cold. Became delirious a half hour thereafter, tossed about on bed; about one hour afterward fell asleep, with heavy breathing. Died at 6 a. m., no convulsions, no vomiting or diarrhea having occurred. Postmortem made twenty-four hours after death showed no evidence of skin rash; pupils not dilated to any special degree; lungs slightly distended and showing hypostatic congestion in posterior portion; numerous small petechiæ over pericardium; slight passive hyperemia of liver. A portion of the stomach contents, amounting to 130.5 grams, was submitted for analysis. This consisted of poorly masticated food, mostly vegetables and about 20 kidney-shaped seeds 2 mm. long and 2.5 mm. wide and of a brownish color; 2.2 mg. of an alkaloid giving Vitali's test were extracted. This alkaloid produced mydriasis in animals. Gave an amorphous precipitate with Wormley's reagent, but became crystalline on standing. This precipitate was insoluble in acetic acid and sparingly soluble in hydrochloric acid.⁷

¹ McGowan, Lancet, London, 1890, ii, 175.

² E. H. Lipscomb, Brit. Med. and Surg. Jour., 1888, i, 694.

³ G. H. Biden, Brit. Med. Jour., 1891, i, 284.

⁴ Coughlin, New York Med. Jour., 1912, xcv, 177. For other cases of belladonna poisoning see Bing, Brit. Med. Jour., 1909, ii, 1282; Bijlana, Geneesk. Courant, 1909, lxi, 396; Kanngiesser, Münch. med. Wehnschr., 1911, lviii, 2505; Nathan, Brit. Med. Jour., 1914, i, 965; Hunzicker, Cor. Bl. f. Schweiz. Aerzte, 1916, xlv, 684; Joll, Lancet, 1916, ii, 647; von Braitenberg, Wien. klin. Wehnschr., 1916, xxix, 1651; Crawford, Brit. Med. Jour., 1917, ii, 184; Kolb, Deutsch. med. Wehnschr., 1918, xlv, 1197; Arima, Arch. f. exper. Path. u. Pharm., 1918, lxxxiii, 1 and 157; Quarnstrom, Fiuska läk. sällsk. handl., 1919, lxi, 131; Firth and Bentley (Lancet, 1921, 2, 901) report a case of belladonna poisoning from eating rabbit, which is itself immune to the action of belladonna.

⁵ J. M. Pace, Med. and Surg. Reporter, 1881, xlv, 26.

⁶ H. Terry, Boston Med. and Surg. Jour., 1882, cvi, 123.

⁷ McNally, Jour. Amer. Med. Assoc., 1915, lxxv, 1640. For other cases of stramonium poisoning see Mehta, Indian Med. Gaz., 1904, xxxix, 20; Noc, Ann. d'hyg. et méd. colon., 1903, vi, 327; Lenoir, Ibid., 1908, xi, 167; Gimlette, Brit. Med. Jour., 1907, i, 1138; Petersen, Ugesk. f. Laeger, 1910, lxxii, 1586; Shoemaker, Med.-Phar. Critic, 1910, xiii, 132; Bowman, Bull. Manila Med. Soc., 1911, iii, 1; Mukopadhya, Indian Med. Gaz., 1913, xlviii, 312; Desesquelle, Bull. d. sc. pharmacol., 1908, xv, 704; Scherwinsky, Med. Klin., 1912, viii, 62; Mühlfelder, Deutsch. med. Wehnschr., 1912, xxxviii, 778; Neyron, Lyon méd., 1912, cxix, 556; Parkinson, Austral. Med. Gaz., 1912, xxxi, 187; Howle, Ibid., 1914, xxxv, 341; Bose, Indian Med. Gaz., 1916, ii, 348; van Ravenswaay, Nederl. Tijdschr. v. Geneesk., 1921, i, 298; Solmsen, Münch. med. Wehnschr., 1921, lxxviii, 852; Scott, Penn. Med. Jour., 1922, xxvi, 34.

By Hyoscyamus:

CASE 28.—Children ate of the root of *Hyoscyamus niger*. Thirst; redness and heat of skin; hallucinations; incontinence of urine; vomiting. Recovery.¹

By Scopolamin:

CASE 29.—A thirty-three-year-old paranoic took 0.015 gram (about $\frac{1}{8}$ grain) of scopolamin hydrobromid. Three-quarters of an hour later the patient showed the following symptoms: face slightly congested; respiration 16; pulse strong and slow; pupils widely dilated and insensible to light; consciousness clouded; muscular contractions. Treatment: lavage of stomach and administration of camphor. Recovery.²

CASE 30.—Woman of twenty-nine years received, preparatory to operation a hypodermic injection of $\frac{1}{4}$ grain of morphin and $\frac{1}{150}$ grain of scopolamin hydrobromid. About a half hour thereafter she fell asleep with stertorous breathing. Slightly cyanotic and difficultly aroused. Pupils moderately dilated, but reacted to light. Surface of body dry and pale. Superficial reflexes abolished. Pulse and respiration normal, the latter soon becoming shallow and less frequent. Patient died two hours after receiving the injection.³

CASE 31.—This case is the famous "Crippen Case," perhaps the most sensational poisoning case of this generation. Dr. Crippen was tried and convicted of poisoning his wife with hyoscin hydrobromid. Leaving out of consideration certain medical points, which do not bear on this discussion, the main facts were as follows: Remains of a human adult, probably in early or middle life, consisting of heart, lungs, kidneys, stomach, intestines and portions of skin and muscles, mixed with quicklime were found beneath the floor of the coal-cellar of Crippen's house. In the viscera Dr. Willcox found an alkaloid which produced complete paralysis of the pupil for several days in cats. By the Stas-Otto process he obtained a mydriatic alkaloid which gave a purple color with Vitali's test. By purification he found that the alkaloid was not crystalline, but gummy, and with Wormley's reagent gave brown spheres. He, therefore, concluded that hyoscin was present, the quantities found in the various viscera amounting in all to $\frac{2}{3}$ grain of hyoscin hydrobromid. The lungs contained only the merest trace, much less than the other organs. The distribution pointed conclusively to administration by the mouth and excluded the possibility of the alkaloid being of putrefactive origin, as the best preserved organs yielded the largest percentage of the alkaloid.⁴

CASE 32.—A robust man of middle age received prior to proposed operation 0.007 gram ($\frac{1}{16}$ grain) of scopolamin hydrobromid. In a half hour respirations became very slow and artificial respiration was resorted to. Pupils dilated to maximum. Patient became unconscious quickly, but returned to consciousness five hours thereafter. Recovery.⁵

Postmortem Appearances.—The lesions observed after fatal poisoning from members of this group of alkaloids are not at all characteristic. Externally the skin may show evidence of the peculiar scarlatiniform rash, although this is not often reported. The pupils are usually dilated even for many hours after death, as in the case of Greenway,⁶ in which the autopsy was not made until sixty-four and a quarter hours after death; while in other cases no dilatation was ob-

¹ Pipping, Schmidt's Jahrb. der Med., 1885, ccviii, 130; see also Phillipi and Mühle, Münch. med. Wehnschr., 1910, lvii, 2473; Jakobi, Buda-pesti orv. ujsag., 1919, xvii, 187.

² Stolle, Allg. Ztschr. f. Psychiat., 1900, lvii, 151.

³ Ely, New York Med. Jour., 1906, lxxxiv, 799.

⁴ See Jour. Amer. Med. Assoc., 1910, lv, 1744.

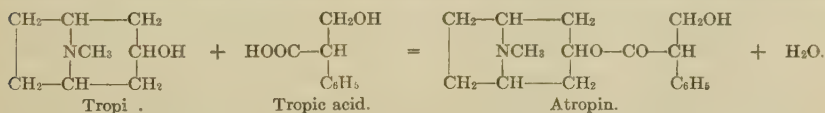
⁵ Zimmermann, Münch. med. Wehnschr., 1912, lix, 423. For other cases of scopolamin poisoning see Kern, Therap. Monatsh., 1891, v, 648; Korff, Münch. med. Wehnschr., 1901, xlviii, 1169; Ibid., 1902, xlix, 1133 and 1408; Blos, Beitr. sur klin. Chir., 1902, xxxv, 565; Kochmann, Therap. der Gegenw., 1903, xlv, 202; de Maurans, Semaine med., 1905, xxv, 529; Calmann, Zentralbl. f. Gynäk., 1910, xxxiv, 471; Nicholson, Lancet, 1910, ii, 884; Heffter, Therap. Monatsh., 1919, xxxiii, 387. For homatropin cases see Brav, Penn. Med. Jour., 1909, xii, 569; Whinna, Homeop. Eye, Ear, and Throat Jour., 1909, xv, 345; Franck, Münch. med. Wehnschr., 1912, lix, 761.

⁶ Brit. Med. Jour., 1878, ii, 516.

served at the postmortem table.¹ The lungs are usually congested or edematous, although there may be simply a hypostatic congestion. The pleural cavities may contain considerable serum. The throat, trachea, and esophagus may be hyperemic; the mucous membrane of stomach and small intestine may be congested, especially if the seeds or other parts of the plant have been taken; and the liver may show slight passive hyperemia. The meninges and brain tissue are markedly congested, while the ventricles of the brain contain much bloody serum.

Properties and Tests.—While the various members of the atropin family of alkaloids show much similarity, both as regards their toxicologic action and chemical properties, yet their recognition and differentiation is possible owing to certain chemical attributes possessed by each of them. It is true, however, that in the usual toxicologic case some of these chemical factors cannot be employed, as the amount of material with which the analyst works is entirely inadequate. Further, the possibility of saponification, conversion of one alkaloid into another, or even entire loss of the alkaloid must be borne in mind.

Atropin ($C_{17}H_{23}NO_3$).—This alkaloid is the chief one of *Atropa belladonna*, although hyoscyamin is present in varying amount together with much smaller quantities of scopolamin, atropamin, and belladonnin. Atropin is a tropein, consisting of a combination of tropin ($C_8H_{15}NO$) with tropic acid ($C_9H_{10}O_3$), hence called tropin tropate. This combination may be graphically represented as follows:



If tropic acid² be heated with dehydrating agents it loses a molecule of water and becomes atropic acid, $C_9H_8O_2$. This latter acid forms with tropin the base atropamin (apoatropin), which is occasionally found in belladonna. Inasmuch as hyoscyamin is readily converted into atropin by heating to 110°C . (230°F .) in absence of air³ or by simply allowing an alcoholic solution to stand after addition of a few drops of alkali,⁴ it is a difficult matter to state just how much atropin and hyoscyamin are originally present in the crude drug.

As hyoscyamin is optically active and atropin inactive, it follows that this difference in the isomers is due to the tropic acids present in their molecules, as tropin is inactive. Hyoscyamin, on saponification with water, splits into tropin and tropic acid, but this tropic acid differs from the optically inactive isomeric one obtained from atropin in being levorotatory.⁵ If this saponification be made with acids or alkalies, the active tropic acid becomes inactive and assumes the racemic form, giving the same splitting products obtained from atropin. It

¹ See Brunetière, Arch. d'anthrop. crim., 1907, xxii, 168; also McNally, Jour. Amer. Med. Assoc., 1915, lvi, 1640.

² McKenzie and Wood, Jour. Chem. Soc., 1919, cxv, 828.

³ Will, Ber. d. d. chem. Gesellsch., 1888, xxi, 1717 and 2777; Schmidt, Ibid., 1829.

⁴ Hesse, Ann. der Chem., 1900, cccix, 75.

⁵ Merck, Arch. der Pharm., 1883, cccxxi, 115.

is evident, therefore, that atropin is simply a racemic modification of tropin.¹ Gadamer² has shown that hyoscyamin, in alcoholic solution, even without addition of alkali is converted into atropin. Amonomiya³ has proved that atropin is converted into tropin and *r*-tropic acid, and that the latter substance may be changed into *d*- and *l*-tropic acid⁴ and then made to combine with tropin, forming *d* and *l* tropates. Atropin is, hence, correctly styled the racemic tropic acid ester of inactive tropin.

Atropin is optically inactive and crystallizes from alcohol or chloroform in white, odorless, rhombic plates, which melt between 114° and 116° C. (237.2° to 240.8° F.). It dissolves⁵ in 455 mls. of water at 25° C. (77° F.) and in 90 mls. of water at 80° C. (176° F.); in 2 mls. of alcohol at 25° C. (77° F.) and 1.2 mls. at 60° C. (140° F.); in about 27 mls. of glycerin; in 1 mil. of chloroform, and in 25 mls. of ether at 25° C. (77° F.). Readily soluble in amyl alcohol and benzene, but very sparingly in petroleum ether. Its saturated aqueous solutions are alkaline to litmus and to phenolphthalein.

It is precipitated from its acidified aqueous solutions by the general alkaloidal reagents, with exception of platinic chlorid, which reacts only in concentrated solutions of the alkaloid. With gold chlorid it produces, when in dilute hydrochloric acid solution, a *characteristic lusterless precipitate of atropin-gold-chlorid* ($C_{17}H_{23}NO_3 \cdot HCl \cdot AuCl_3$). This double-salt is best prepared by adding the aqueous solution of gold chlorid to the hot dilute hydrochloric acid solution of the alkaloid. The precipitate first appears as an oil, but soon becomes crystalline. This salt melts at 135° to 137° C. (275° to 278.6° F.), and yields 31.35 per cent. gold on combustion.

The official atropin sulphate ($C_{17}H_{23}NO_3$)₂H₂SO₄, occurs as a white crystalline powder or as needles or prisms. It is odorless and is efflorescent; 1 part of this salt dissolves in 0.4 mls. of water; 5 mls. of alcohol; 2.5 mls. of glycerin; 420 mls. of chloroform, and in 3000 mls. of ether at 25° C. (77° F.); also in 2.5 mls. of boiling alcohol. Its aqueous solutions are neutral to litmus. It melts between 188° and 191° C. (370.4° to 375.8° F.) as usually found, but when anhydrous and free from hyoscyamin melts between 181° and 183° C. (357.8° to 361.4° F.). Richmond⁶ states that the melting-point is 194° C. (381.2° F.).

Homatropin ($C_{16}H_{21}NO_3$).—This tropein is an artificial or synthetic alkaloid obtained by the condensation of tropin ($C_8H_{15}NO$) with mandelic acid ($C_8H_5O_3$) in presence of hydrochloric acid. It is, therefore, chemically known as tropin mandelate and is the next lower homologue of atropin, hence the name homatropin. It crystallizes from absolute ether in prisms, which are very hygroscopic and melt between 95.5° and 98.5° C. (203.9° to 209.3° F.). The alkaloid itself is not used in

¹ Ladenburg, Ber. d. d. chem. Gesellsch., 1880, xiii, 109, 254 and 607.

² Arch. der Pharm., 1901, cccxxxix, 294, 321 and 663.

³ Ibid., 1902, cexl, 498.

⁴ Ladenburg and Hundt, Ber. d. d. Chem. Gesellsch., 1889, xxii, 2590.

⁵ Here, as elsewhere, the solubilities and physical characteristics of the alkaloids are given when possible, in terms of the U. S. Pharmacopœia, 9th revision, 1916. One mil. is equivalent to 1 c.c.

⁶ Amer. Jour. Pharm., 1918, xc, 661.

medical practice, the official salt being the hydrobromid. This latter compound ($C_{16}H_{21}NO_3HBr$) occurs as a white, odorless, crystalline powder or in rhombic prisms; 1 gram of homatropin hydrobromid dissolves in 6 mls. of water; in 40 mls. of alcohol, and in 420 mls. of chloroform at $25^\circ C.$ ($77^\circ F.$); also in 12 mls. of alcohol at $60^\circ C.$ ($140^\circ F.$); insoluble in ether. Its aqueous solution is neutral to litmus. The salt melts at about $212^\circ C.$ ($413.6^\circ F.$) with partial decomposition. The general alkaloidal reagents, with exception of tannic acid and platinic chlorid, precipitate it from its dilute aqueous solution. The alkaloid responds to Gerrard's reaction, but not to Vitali's test (see below).

Hyoscyamin ($C_{17}H_{23}NO_3$).—This alkaloid is the chief basic substance of *Hyoscyamus niger*, but is also present, in varying amounts, in belladonna and stramonium. As stated above, hyoscyamin is an isomer of atropin, into which it is easily converted by various means. Like atropin it is a tropein, being a combination of tropin with levorotatory tropic acid. Hence, chemically speaking, hyoscyamin is the levo-tropic acid ester of inactive tropin.

Hyoscyamin crystallizes from alcohol or benzene in needles, which have a melting-point of $108.5^\circ C.$ ($227.3^\circ F.$). It is difficultly soluble in water, readily soluble in alcohol, ether, amyl alcohol, chloroform, and benzene. Its aqueous solutions are alkaline to litmus and phenolphthalein. It is levorotatory, showing a specific rotation at $15^\circ C.$ ($59^\circ F.$) of $[\alpha]_D = -20.3$. Like atropin, it is precipitated from its acidulated aqueous solutions by the general alkaloidal precipitants, with exception of platinic chlorid. With gold chlorid it produces, when in dilute hydrochloric acid solutions, a *characteristic precipitate in the form of minute, lustrous golden-yellow scales of hyoscyamin-gold-chlorid* ($C_{17}H_{23}NO_3HClAuCl_3$), melting at $162^\circ C.$ ($323.6^\circ F.$), and yielding 31.35 per cent. of gold. This salt differs from the corresponding one formed with atropin in not first precipitating as an oil.

The official hyoscyamin hydrobromid ($C_{17}H_{23}NO_3HBr$) occurs in white prismatic crystals without odor, but deliquescent on exposure to air; 1 gram of this salt dissolves in 2.5 mls. of alcohol; in 1.7 mls. of chloroform, and in 2260 mls. of ether at $25^\circ C.$ ($77^\circ F.$); very soluble in water. Its aqueous solution is neutral to litmus and is strongly levorotatory. It melts at about $152^\circ C.$ ($305.6^\circ F.$).

Scopolamin ($C_{17}H_{21}NO_4$).—This alkaloid is probably identical with hyoscin, although some writers believe it to be the optically inactive form (racemic modification), while hyoscin is the levorotatory form.¹ It differs from the other members of this series in not being a tropein. Although a derivative of tropic acid, the base in combination with this acid is not tropin but scopolin ($C_8H_{13}NO_2$), sometimes called oscin. This latter base varies from tropin in the replacement of 2 H. atoms by 1 oxygen atom, which substitution is probably in ether-like combination. It is, therefore, scopolin tropate.

This alkaloid is found in belladonna, stramonium, and hyoscyamus, as well as in the unofficial *Scopolia japonica*. It is an amorphous sub-

¹ See King, Jour. Chem. Soc., 1919, cxv, 476 and 974.

stance, difficultly soluble in water, but soluble in alcohol, ether, chloroform, and benzol. It is precipitated from its aqueous solutions by most of the general alkaloidal reagents. With gold chlorid it forms scopolamin gold-chlorid, a double salt which crystallizes in large rhombic prisms, melting at 198° to 199° C. (387.4° to 390.2° F.), and yielding 30.65 per cent. of gold.

The official hydrobromid ($C_{17}H_{21}NO_4HBr + 3H_2O$) occurs in colorless, transparent, rhombic crystals, sometimes of large size; odorless; slightly efflorescent; 1 gram of this salt dissolves in 1.5 mls. of water and in 20 mls. of alcohol at 25° C. (77° F.); slightly soluble in chloroform; insoluble in ether. Its aqueous solution is neutral or at most only slightly acid to litmus. When anhydrous it melts at 190° to 192° C. (374° to 377.6° F.). It is levorotatory, showing a specific rotation at 25° C. (77° F.) in a 100 mm. tube of -22° to -25.75° .

For the identification of this group of alkaloids the special tests of value are—(1) the physiologic tests; (2) the color tests of Vitali and

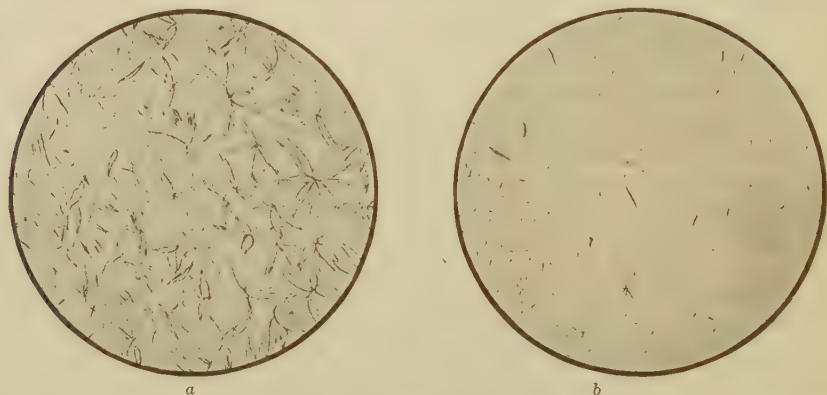


Fig. 47.—Atropin treated with bromin: *a*, $\frac{1}{100}$ grain atropin in 1 grain water ($\times 75$); *b*, $\frac{1}{10000}$ grain atropin in 1 grain water ($\times 125$).

of Gerrard; (3) crystalline form of the bromin compound; (4) the Gulielmo-Sohn reaction for products of aromatic odor, and (5) crystalline form, melting-point, and percentage of gold of the chloraurates.

Biologic Tests.—1. **Upon the Eye.**—The eye of man or of a cat may be employed for this purpose. The human eye is far more sensitive to the action of these alkaloids than is the feline, but if the test is to be applied to the human eye somewhat more care should be taken to obtain a pure product. Prepare an aqueous solution of a portion of the purified residue, obtained by the extraction processes. This solution should not be acid nor more than very slightly alkaline (due to the normal alkalinity of the alkaloid). While some prefer to use the neutral solution, this is not at all necessary. One or 2 drops of this solution are introduced from a pipet into the corner (inner canthus) of one eye, the pupil of which is compared in size with its fellow from time to time. In the results of Squibb¹ with the eye of man, using one drop of the

¹ Ephemeris, 1885, ii, 855.

solution, a dilution to 2280 parts gave commencing dilatation in from fifteen to eighteen minutes; a dilution to 4560 parts in thirty minutes. It would appear, therefore, that $\frac{1}{20000}$ grain (0.00003 gm.) of the alkaloid in a drop of solution is sufficient to show dilatation in about half an hour. Feddersen¹ fixes the minimum quantity of atropin sulphate which will distinctly dilate the pupil of a human adult at 0.0002 mg. (0.000003 gr.); while Fühner² states that 0.01 mg. causes a slight dilatation of the pupil of a cat.

This mydriatic effect is shown by all members of this group, the degree of dilatation depending on the dose and time of observation. The dilatation with homatropin appears somewhat more quickly, is less complete, and passes off sooner than that with atropin. It is to be remembered that mydriasis is not sufficient in itself to warrant a conclusion that a specific residue contains a member of this group of alkaloids, as cocain, adrenalin, and ptomatropins produce a similar result. Thus, Zülzer and Sonnenschein³ isolated from decomposing tissue, by extraction of the alkaline solution with ether, a basic substance which formed microscopic crystals, produced mydriasis, and increased the action of the heart. Brieger⁴ has also isolated another putrefactive basic product (called mydalein), which produced mydriasis.

2. Upon the Heart.—This reaction is based on the antagonistic action of atropin and muscarin upon the terminations of the vagus nerve in the cardiac musculature. If the heart of a large water-frog be exposed and a few drops of muscarin solution be passed through a cannula into the heart or be dropped directly on the heart muscle, a gradual slowing of the action is observed with final arrest in diastole. If, now, the muscarin be washed out of the heart and a small amount of an aqueous solution of atropin be added (or if atropin solution be applied directly to the muscle), the heart will begin to pulsate and soon become quite rapid. According to Harnack,⁵ $\frac{1}{4000}$ mg. of atropin administered to a frog will overcome the affect of muscarin. Fleischmann⁶ has modified this method so that as small an amount as a $\frac{1}{100000000}$ gram may be detected.

Chemical Tests.—**1. Vitali's Test.**—This⁷ is one of the most reliable tests for the members of this group of alkaloids. Either the solid alkaloid or any of its salts, with exception of the hydrochlorid,⁸ may be used. In a small porcelain evaporating dish place some of the residue obtained in the extraction process, or evaporate a portion of

¹ Beitrag zur Atropinvergiftung, Dissert., Berlin, 1884, 37.

² Nachweis und Bestimmung von Giften auf biologischem Wege, Berlin, 1911, pp. 162, 165.

³ Berl. klin. Wehnschr., 1869, vi, 121.

⁴ Ptomaine, ii, 48.

⁵ Arch. f. exp. Path. und Pharmakol., 1874, ii, 331.

⁶ Berl. klin. Wehnschr., 1911, xlviii, 135. Togawa (Biochem. Ztschr., 1920, cix, 43) calls attention to the apparently specific action of atropin in preventing the increased flow of saliva normally following intravenous injection of vitamins.

⁷ Jour. de méd., de chir., et de pharm., 1880, lxxi, 66, 161, 167, 279 and 382; Manuale di chimica tossicologica, 1893, 382; Chem. Centralbl., 1894, ii, 816; Boll. Chim. Farm., 1894, iv, 449.

⁸ See Chapuis, Precis de Toxicol., 1889, 631.

the aqueous solution, add a few drops of fuming nitric acid and evaporate to dryness on the water-bath. Allow the colorless or, at most, very slightly yellow residue to cool and add a few drops of fresh alcoholic potassium hydrate solution. A fine violet color is produced, soon fading to dark red and then disappearing. This color may be made to reappear by adding more alcoholic potash. This test is said to be given by 0.001 mg. of atropin. It reacts, with similar results, to atropin, hyoscyamin, and scopolamin, but not to homatropin.

Instead of applying the test in the above manner, *Arnold's modification*¹ may be employed, as follows: The dry residue on white porcelain is barely moistened with concentrated sulphuric acid at the point of a narrow glass rod, when a little solid sodium nitrite is added and rubbed into the mixture without spreading it needlessly. To this slightly yellowish spot add a few drops (in excess of the acid) of fresh alcoholic potash, when there is observed a violet color, fading to reddish violet, dark red, pale rose, and finally disappearing. Flückiger² employs sodium nitrate instead of the nitrite. With this Arnold's modification all of the members of this group, including homatropin, react identically.

This reaction of Vitali is fairly characteristic for this group of mydriatic alkaloids, especially if the sequence of colors given above is obtained. Other alkaloids, such as pseudo-aconitin, veratrin, and strychnin, may possibly interfere with or mask the typical Vitali reaction, yet other reactions of this mydriatic group as well as the reactions for the other alkaloids mentioned will easily differentiate them.³ Further, strychnin gives only the initial violet and soon changes into orange and brownish red, a sequence which is not observed with atropin. Besides the above alkaloids, which give misleading reactions with this test, certain ptomatropins may produce somewhat similar colorations. Thus, the basic substance, isolated by Giotto and Spica,⁴ responded to this test, but was easily differentiated from the true alkaloids by not producing mydriasis. It is important, therefore, in deciding as to the value of any special color reaction to remember that a single reaction should not be made the basis for an unequivocal report as to identity. It is, also, essential to insist that the sequence of the color changes, and not simply the initial coloration, be identical before reactions of different alkaloids may be considered the same. If this be done, much confusion will be avoided.

2. Gerrard's Test.—To a portion of the purified residue (obtained in the extraction processes) add 1 to 2 c.c. of a 2 per cent. solution of mercuric chlorid in 50 per cent. alcohol. Warm gently, when the residue becomes yellow and finally brick-red in color due to precipitation of mercuric oxid (with a trace of mercurous oxid).⁵

¹ Ztschr. f. anal. Chem., 1884, xxiii, 231; Arch. der Pharm., 1882, xx, 561.

² Pharm. Jour. and Trans., 1888, xvi, 601; Chem. Centralbl., 1886, 504.

³ In this connection see Beckmann, Arch. der Pharm., 1886, xxiv, 481; Thoms, Pharm. Centralbl., 1890, xxxi, 559; Menegazzi, Boll. Chim. Farm., 1894, iv, 103.

⁴ Pharm. Centralbl., 1891, xxxii, 26.

⁵ Gerrard, Pharm. Jour. and Trans., 1883-84, xiv, 718 and 729; Ibid., 1891, xxi, 898.

This coloration and precipitation appear at once with atropin; while with hyoscyamin the reaction comes out more slowly. If an excess of hyoscyamin be present, only a yellow precipitate is formed; while with a large excess of the reagent no precipitation occurs. For these reasons, Schweissinger¹ recommends the addition of only a few drops of the reagent to a residue suspected of containing hyoscyamin. Homatropin reacts positively to this reagent, while scopolamin gives neither a yellow nor red precipitate. Gerrard reports white precipitates, which may become slightly yellow on heating with strychnin, brucin, morphin, codein, veratrin, aconitin, coniin, gelsemin, caffenin, cinchonin, cinchonidin, quinin, and quinidin. Flückiger states that cocain gives a pure white precipitate, which soon turns red.²

3. **Wormley's Bromin Test.**—An aqueous solution of hydrobromic acid saturated with bromin produces with atropin or hyoscyamin and their salts, even in such dilute solutions as 1 : 10,000, a yellow amorphous precipitate which becomes crystalline in a short time. This precipitate is insoluble in acetic acid and only very sparingly soluble in excess of mineral acids or fixed caustic alkalies. From strong solutions of the alkaloid the precipitate may disappear, but this may be reproduced by addition of more of the reagent.³

While most alkaloids produce yellowish precipitates with this reagent, none become crystalline except those with members of this group, with meconin, and possibly, with veratrin. In the case of atropin and hyoscyamin, the precipitate assumes a characteristic form, appearing in bunches of needles or as lanceolate leaf-like crystals grouped together like the petals of a flower (Fig. 47). If the solution be very dilute, the crystals are still distinct but not so clearly defined. Scopolamin produces with this reagent a precipitate of minute brownish globules, which under certain circumstances (not in solutions extremely dilute) may change to groups of bold crystals quite different from those obtained with atropin. Carr⁴ states that the crystals with scopolamin are tabular in form and are often arranged in leaf-like rosettes, even in dilutions of 1 : 2000. He, further, indicates that homatropin and caffenin give crystalline precipitates with Wormley's reagent.

For microscopic purposes this test may be made by adding a drop of the reagent to a drop or two of an aqueous solution of the salt of the supposed alkaloid on a glass slide. Spontaneous evaporation of the liquid will usually result in the formation of the characteristic crystals, which may be observed under the microscope.

4. **Gulielmo-Sohn Reaction.**—If $\frac{1}{64}$ grain (1 mg.) of atropin be heated in a small test-tube until white vapor arises, then about 1 c.c. of concentrated sulphuric acid be added and heated until the acid begins to color, and then, after cooling sufficiently, about 2 c.c. of

¹ Pharm. Zeitung, 1884, xxix, 683.

² Pharm. Jour., 1886, xvi, 601.

³ Wormley, Micro-Chemistry of Poisons, 2d ed., 1885, 642; Amer. Jour. Pharm., 1894, lxvi, 513.

⁴ Atropin and its Allies, in Allen's Commercial Organic Analysis, 1912, vi, 308.

water be added drop by drop along the side of the tube, an odor suggestive of flowers will be obtained. If a small crystal of potassium permanganate be introduced before the water is added, the odor will be like that of bitter almonds.¹

5. DIFFERENTIAL TESTS²

Alkaloid.	Reaction to phenolphthalein.	Mydriasis.	Vitali's test.	Arnold's test.	Gerrard's test.	Crystalline form, melting-point, and percentage of gold in the chloraurates.	Wormley's reagent.
Atropin.	Positive.	Positive.	Positive.	Positive.	Positive.	Lusterless precipitate. Melting-point 135° to 137° C. Gold = 31.35 per cent.	Needles or lanceolate crystals.
Hyoscyamin.	Positive.	Positive.	Positive.	Positive.	Positive.	Lustrous golden yellow scales. Melting-point 162° C. Gold = 31.35 per cent.	Needles or lanceolate crystals.
Scopolamin.	Positive.	Positive.	Positive.	Positive.	Negative.	Large rhombic prisms. Melting-point 198° to 199° C. Gold = 30.65 per cent.	Minute brownish globules or tabular crystals.
Homatropin.	Positive.	Positive.	Negative.	Positive.	Positive.	Yellow prisms. Gold = 32.05 per cent.	Crystalline precipitate not characteristic.

Pharmacognosic Tests.—If poisoning from swallowing the seeds of stramonium or of hyoscyamus or the berries of belladonna be in question, the contents of the stomach should be closely inspected for parts of the seeds or the whole unbroken seeds. The stramonium seeds are flattened, kidney shaped, dull black or brownish-black in color, about 2 mm. long, and 2.5 mm. wide, and marked externally with a network showing punctate depressions. The seeds of hyoscyamus are smaller than the above (about 1 mm. long), kidney shaped, roughened, gray or grayish-brown in color. Belladonna seeds are about 3 mm. long, kidney shaped, brown or gray in color, and less rough exteriorly than those of hyoscyamus.

¹ Gulielmo, Schweiz. Wehnschr. f. Pharm., 1863, 1, 146; Sohn, Dictionary of the Active Principles of Plants, 1894, 15.

² See Eder, Schweiz. Apoth. Ztg., 1916, liv, 501, 517, 534, 544, 560, 609, 621, 657, 669, 685, and 717; Wasicky (Ztschr. f. anal. Chem., 1915, liv, 393; see also Jour. pharm. chim., 1917, xv, 54) advises the following test for the solanaceous alkaloids: Dissolve 2 gm. of para-dimethyl-amino-benzaldehyd in 6 gm. of concentrated sulphuric acid and carefully add 0.4 gm. of water. This combination forms a dark yellow liquid, which keeps well for two weeks. If a trace of solanaceous alkaloid be warmed with 1 drop of the above reagent, a very intense red violet color is produced. Atropin, hyoscyamin, and scopolamin behave identically to this test, which is sensitive to a dilution of 2×10^{-4} mg., although homatropin does not respond.

The Separation of Atropin, Hyoscyamin, etc., from Animal Tissues.—The material in a weighed portion is finely divided by playing upon it in a good-sized evaporating dish with a pair of large shears of bright surface or by the use of a hashing machine. The divided material is digested (at a temperature not over 50° C.—122° F.) with five or six volumes of diluted alcohol (about 50 per cent.), with the slightest acidulation by tartaric or acetic acid, stirring constantly for half an hour. The mixture is strained, the residue digested about eight minutes with a smaller portion of the same solvent, and strained again, washing with a third and smaller portion of the solvent. The mixed alcoholic solutions are digested while stirring on the water-bath for fifteen or twenty minutes, adding a little full-strength alcohol from time to time, nearly to complete the precipitation caused by the alcohol, when the mixture is strained and the residue washed with a little alcohol of about the same strength as that of the filtrate. The liquid is now treated with sufficient calcined magnesia to take up the free acid, and concentrated by distilling rapidly in the vacuum obtained by a water-pump¹ as long as the liquid remains limpid. It is now strained and the residue washed with a little solvent of about the same alcoholic content as the filtrate. The latter, if too much loaded with tissue matters, so as to cause the liquid to emulsify in shaking out afterward, may be treated with full-strength alcohol, filtered—better by use of a filter-pump and a Buechner funnel—and the filtrate concentrated as before.

The extraction, however varied, should be so governed as to avoid, so far as possible, the conditions of hydrolysis.

The final aqueous liquid, which may be slightly alcoholic, filtered clear, is gently shaken in a separator with chloroform, then made only perceptibly alkaline by the addition of ammonia, again shaken (not so violently as to cause emulsification) for about five minutes, when the crude chloroform extract is drawn off, and in the same way a second and a third portion obtained. The total crude chloroform extract is now shaken out with water very slightly acidulated with sulphuric acid in three portions, and at once the total water solution is shaken with chloroform, then made just alkaline with ammonia, and shaken successively with three portions of chloroform. If, on evaporation, a small portion of the last chloroform extract shows the presence of obstructing tissue matter, the purification is repeated, beginning with the treatment by acidulated water, until a purified chloroform extract is obtained. This is to be concentrated, and then portions of a drop or two or three are separately evaporated to dryness for final tests, as specified under the head of Chemical Tests.

To estimate the quantity of atropin in the extract, its precipitation as a periodid, in the gravimetric method, is probably the most expedient way. The alkaloidal solution is *added to an excess* of decinormal aqueous iodine solution with potassium iodide, the precipitate well stirred, drained, washed, dried, and weighed as atropine hydriodide octa-iodide. When this weight is multiplied by 0.202, the product expresses

¹ The apparatus shown in Fig. 10, p. 60, is useful for this purpose.

the quantity of atropin as free alkaloid.¹ Any estimate of the quantity of atropin in the tissues must depend upon an estimation of the loss of the alkaloid in the process of extraction, and if this be more than conjecture, it must be based upon the loss of alkaloid in a parallel analysis made for control.

Deposition in the Body.—Wormley recovered atropin from the blood after administering the drug to dogs and cats. The tropeins generally appear in the urine of persons poisoned by them. Atropin has been repeatedly recovered from putrefactive animal tissues, in which it does not readily decompose. Ipsen² isolated 0.2642 gram (4.077 gr.) of pure crystalline atropin sulphate from a cadaver after more than three years' burial. After its administration, Dragendorff detected atropin in the urine, in the liver, and in the kidneys of the cat, but none was found in the spleen. It was found in the blood of a cat weighing 6 pounds (2800 gm.) twenty-four hours after 2.8 grains (0.1863 gm.) of the alkaloid had been administered by the mouth, with ligation of the esophagus. The same investigator gave 1 grain (0.06 gm.) of atropin daily to a rabbit of 3½ pounds (1500 gm.). Each day the urine was found to contain much atropin. On the tenth day the blood was tested and mere traces of the alkaloid found in it. In a similar experiment like results were obtained in the urine, but no alkaloid was found in the feces.

COCAIN AND COCAIN SUBSTITUTES

General Description and Relations.—Cocain ($C_{17}H_{21}NO_4$) is the chief alkaloid of the leaf of *Erythroxylon coca*, constituting about 0.75 per cent. of the freshly dried leaf. This plant is indigenous in South America, but has been introduced into India, Ceylon, and Java. Besides cocain, several other alkaloids are found in this leaf, such as hygrin, cinnamyl-cocain, α -truxillin (cocamin), β -truxillin, benzoyl-ecgonin, and tropacocain. Few of these latter alkaloids have any special physiologic or toxicologic value, while cocain finds wide use in medicine as a local anesthetic and has been very extensively misused as a habit-forming drug. While crude cocain is shipped from South America, it does not find a place in the market, as it must be highly purified before being medicinally employed.

Cocain was first isolated by Niemann³ from the peruvian coca leaves. On saponification with water cocain splits into methyl alcohol and a base, benzoyl-ecgonin; while this base is further split into benzoic acid and ecgonin if the saponification be conducted with mineral acids or alkalies, as follows:



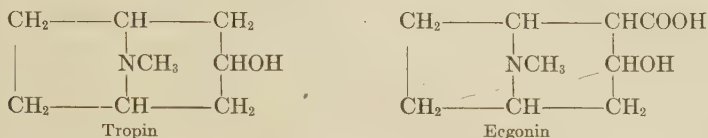
Cocain is, hence, the methyl-benzoyl ester of ecgonin.

¹ Prescott and Gordin, Atropin Periodids, etc., Jour. Amer. Chem. Soc., 1898, xx, 329; Ibid., Volumetric Estimation of Alkaloids, etc., xx, 712, 722, 724.

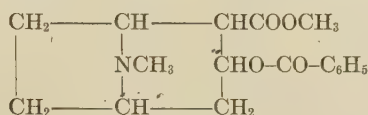
² Vrtljschr. f. ger. Med., 1906, xxxi, 308.

³ Ann. der Chem., 1860, cxiv, 218.

Like tropin (see Atropin) ecgonin belongs to the tropan-ring system and differs from tropin only in the replacement of a hydrogen atom of the second atomic group by the carboxyl group, thus:



Cocain may be represented graphically, therefore, by the following formula:



The close relationship, chemically, between cocain and atropin is shown by the similarity of their basic groups. Possibly this chemical relationship may account for certain similarities in pharmacologic action. It is interesting to note that one may readily synthesize¹ atropin, beginning with cocain, passing through the stages of ecgonin, anhydro-ecgonin, tropidin, and tropin to atropin.

Corresponding to the different stereoisomeric ecgonins, cocain exists in three stereoisomeric forms, l-cocain, d-cocain, and r-cocain, while a fourth cocain, known as a-cocain, has the carboxyl and hydroxyl groups attached to the same carbon atom.² It will thus be seen that the optical activity of the cocains rests in the basic part of the molecule, while that of the atropin group is resident in the acid portion. The l-cocain is possessed of certain medicinal properties which are not common to the other derivatives.

l-Ecgonin ($\text{C}_9\text{H}_{15}\text{NO}_3 + \text{H}_2\text{O}$) crystallizes with 1 molecule of water in rhombic prisms, melting at 198°C . (388.4°F). It is neutral in reaction, readily soluble in water, difficultly soluble in absolute alcohol or chloroform, and insoluble in ether. Its chloraurate crystallizes from alcohol in monoclinic prisms with $2\text{H}_2\text{O}$, and when anhydrous, melts at 202°C . (395.6°F).

l-Benzoyl-ecgonin ($\text{C}_{16}\text{H}_{19}\text{NO}_4 + 4\text{H}_2\text{O}$) crystallizes with 4 molecules of water, in transparent, flat prisms, melting when anhydrous at 189° to 193°C . (372.2° to 379.4°F). It is difficultly soluble in cold water and ether, but soluble in alcohol, methyl alcohol, and in hot

¹ See Merck, Ber. d. d. chem. Gesellsch., 1885, xviii, 2264 and 2952; Skraup, Monatsh. f. Chem., 1885, vi, 556; Gadamer and John, Arch. Pharm., 1921, 259, 227.

² For special chemical references see Einhorn, Ber. d. d. chem. Gesellsch., 1887, xx, 1221; 1888, xxi, 47 and 3335; 1889, xxii, 399, 1362 and 1495; 1890, xxiii, 468, 979 and 1338; 1893, xxvi, 324, 962 and 1482; 1894, xxvii, 1523, 1874, 2447 and 2960; C. Liebermann, Ibid., 1888, xxi, 2342 and 3196; 1889, xxii, 130, 672, 675, 680 and 2661; 1890, xxiii, 141, 508, 512, 926 and 2518; 1891, xxiv, 407, 606, 1101, 2336 and 2587; 1892, xxv, 927; 1893, xxvi, 834; 1894, xxvii, 1416, 2037 and 2051; Willstätter, Ibid., 1896, xxix, 2216; 1897, xxx, 2679; 1898, xxxi, 1212, 1534, 2498 and 2655; 1899, xxxii, 1637; Ann. der Chem., 1903, cccxxvi, 42; Willstätter and Müller, Ber. d. d. chem. Gesellsch., 1898, xxxi, 1203; Braun, Ibid., 1908, xli, 2122; Schmidt, Pflanzenalkaloide, Biochemisches Handlex., 1911, v, 68 and 93 et seq.

water, acetone, and chloroform. It is neutral in reaction. This compound has no anesthetic effect when applied to the eye, but does exert a moderate mydriatic influence. It is very irritating to the mucous membranes, and when injected subcutaneously may produce tetanic spasms, but does not cause paralysis of the sensory nerves.¹

l-Cocain ($C_{17}H_{21}NO_4$) occurs in large, colorless, four- or six-sided monoclinic prisms or as an odorless, white, crystalline powder, melting between 96° and 98° C. (204.8° to 208.4° F.). One gram of cocain dissolves in about 600 mls. of water; 6.5 mls. of alcohol; 0.7 mil. of chloroform; 3.5 mls. of ether, and 12 mls. of olive oil at 25° C. (77° F.); also in 270 mls. of water at 80° C. (176° F.); very soluble in warm alcohol; slightly soluble in liquid petrolatum. It is levorotatory, $[\alpha]_D = -15.8$. Its solutions are alkaline to litmus, cochineal, iodeosin, and methyl orange, but not to phenolphthalein. It is precipitated by the general alkaloidal reagents, its chloraurate melting at 198° C. (388.4° F.), while its chlorplatinate melts at 122.5° to 123° C. (252.5° to 253.4° F.).

The *official hydrochlorid* ($C_{17}H_{21}NO_4HCl$) occurs in colorless, transparent, monoclinic prisms; in flaky, lustrous leaflets; or as a white crystalline powder; odorless; permanent in the air; melting between 183° and 191° C. (361.4° to 374.8° F.), the higher melting-point indicating greater purity. One gram of the salt dissolves in 0.4 mil. of water; 3.2 mls. of alcohol, and in 12.5 mls. of chloroform at 25° C. (77° F.); also in 2 mls. of alcohol at 60° C. (140° F.); soluble in glycerin; insoluble in ether. Its aqueous solutions are neutral and levorotatory.

Symptoms of Poisoning by Cocain.—The symptoms noted after intake of cocain are the result of a primary stimulation followed by a depression of the central nervous system. Cushny states this as follows: "The action of cocain on the central nervous system is primarily a descending stimulation, the cerebrum being first affected, then the hind brain and medulla oblongata, and, last of all, the spinal cord. Perhaps it might be better expressed by saying that after small quantities the chief symptoms arise from the cerebrum, but as the dose is increased those from the lower parts of the central axis tend to become more prominent. After the stimulation there succeeds depression, which follows the stimulation downward, affecting first the cerebrum and then the lower divisions. The two stages are not definitely divided, however, one part of the cerebrum often showing distinct depression, while another is still in a condition of excessive activity." Cocain also paralyzes the terminations of the sensory nerves, which action is the basis of its use as a local anesthetic.

If a poisonous dose be taken by the mouth, hypodermically, or by absorption through an abraded surface or a portion of the mucous membrane, severe symptoms quickly appear, varying considerably in different individuals. In most cases there is excitement, pleasurable or disagreeable. The patient is generally restless and more talkative than usual, the speech being incoherent or foolish. Not infrequently the mental disturbance may progress to delirium with hallucinations,

¹ See Stockman, *Pharm. Jour.*, 1886, xvi, 898.

or may lead to a violent maniacal condition. Occasionally, however, there may be a calmness with little tendency to sleep, the patient being fully conscious of what is going on around him. There is a feeling of dryness in the mouth, nose, and throat, difficulty in swallowing, and a feeling of suffocation. Nausea is an early symptom, although vomiting is by no means common, and a burning pain in the stomach may be prominent. There may be vertigo or severe pain and burning sensations in the head. Numbness, tingling or prickling of the hands and feet, or an anesthesia at the point of application may be noted. Pulse is accelerated and feeble at first, although the heart may be bounding and tumultuous. Later the heart becomes slow, weak, and irregular. Respirations at first quick and deep, gasping, or even of Cheyne-Stokes' type. Later this becomes slow and shallow, with intermittent periods, with final arrest. Pupils generally dilated and insensible to light, although they may, rarely, be normal or even contracted. The eyes are usually protuberant and show paralysis of accommodation. Reflexes usually somewhat more easily excited than usual and tremors or slight convulsions may occur. Later powerful tonic or clonic convulsions appear. In some cases, however, convulsions are absent and collapse and periods of unconsciousness are noted. Skin is pale and cold in the early stages and covered with a free perspiration (although a few cases of dry skin have been reported); later the skin becomes cyanotic. Death results from gradual respiratory failure. Recovery may be rapid and complete, although extreme prostration may continue for some time.¹

Chronic poisoning, with which may be classed the effects of the cocain habit, is a subject for the physician rather than for the toxicologist. Mancini² reports a fatal case of poisoning in an addict, the suggestion being made that the victim had exceeded his limit of tolerance or that he had previously used adulterated specimens.

Period When Fatal.—In acute poisoning by cocain the symptoms appear very quickly after the poison is absorbed and run a rapid course. It is stated that, generally, if the patient survives half an hour, he recovers³ (see the cases quoted below).

Fatal Quantity.—Cocain is employed medicinally for various purposes and is widely used by habitués in the form of snuff. It is a very difficult matter to state definitely the lethal dose of cocain, owing to the variable susceptibility of different individuals. While Mannheim⁴ considers 1 gram as the lethal dose, whether given by mouth or otherwise, many cases are reported in which larger amounts have not caused death, and, on the other hand, smaller doses have proved fatal. In considering this point the portal of entry of the drug must be regarded as of great importance. Thus, 0.04 gram ($\frac{2}{5}$ gr.) has caused death when given subconjunctivally⁵; 0.648 gram (10 gr.)

¹ See Giroux, *Gaz. d. hôp.*, Paris, 1919, xcii, 245.

² *Riv. Crit. di Clin. Med.*, 1922, 23, 121.

³ Haines in *Hamilton's Legal Medicine*, 1894, i, 428.

⁴ *Ztschr. f. klin. Med.*, 1890, xvi, 380.

⁵ Abadie, *Internat. klin. Rundschau*, 1888, ii, 1746.

when taken by mouth¹; 1.5 grams (23 gr.) by rectum,² and 0.03 gram (0.46 gr.) per urethra.³

Treatment.—When the poison has been taken by the mouth, the first thing to do is to draw off the contents of the stomach by means of a siphon-tube or a stomach-pump, introducing water and drawing it off again, until the stomach is well washed out. If it can be done without delay, finely powdered charcoal may be administered during the evacuation of the stomach.

The symptoms, variable as they are, should be met by the restorative measures directly indicated. Carbonate of ammonium, hot alcoholic drinks, stimulants hypodermically, sinapisms over the heart and stomach, and friction of the extremities are helpful, especially in the cyanotic stage. Haines⁴ states that "inhalations of amyl nitrite and hypodermic injections of nitroglycerin are often signally useful; and inhalations of pure oxygen are very valuable in relieving threatened asphyxia. In case breathing ceases, artificial respiration should be resorted to, and electricity may be tried, with some chance of a favorable result." Mayer⁵ advises the use of calcium chlorid to inhibit the action of cocain.

Statistics.—The earliest reported case of cocain poisoning is the one of attempted suicide mentioned by Plass.⁶ Witthaus⁷ has collected 384 cases up to 1909, of which he states that all prior to 1894, with the above suicidal exception, were accidental, resulting from the use of cocain in surgical practice. Since 1909 we have found reports of 11 further cases. Of this total of 395 cases, 10 were attempted or actual suicide, none homicidal, the remainder accidental⁸; 74 were fatal. Owing to the large increase in the cocain habit during the last few years it is probable that many fatal cases occur annually which are never reported as such.

CASES OF POISONING BY COCAIN

CASES 1-3.—One dram (4 c.c.) of a 4 per cent. solution of cocain (about 2½ grains—0.146 gm.—of the alkaloid) was thrown into the urethra of a man. Convulsions appeared at once, and death occurred in four minutes. The autopsy showed intense congestion of the lungs.

¹ Curgenven, *Quart. Med. Jour.*, 1895, iv, 152.

² Szuman, *Therap. Monatsh.*, 1888, ii, 393.

³ Haynes, *Med. News*, 1894, lxx, 144.

⁴ Walter S. Haines in *Hamilton's Legal Medicine*, 1894, i, 429.

⁵ *Schw. med. Wehnschr.*, 1921, 51, 767. See also Fabry, *Münch. Med. Wehnschr.*, 1922, 69, 969.

⁶ *Ztschr. f. Med. Chir. u. Geburtsh.*, 1863, ii, 222.

⁷ *Medical Jurisprudence, Forensic Medicine, and Toxicology*, 1911, iv, 897.

⁸ See Latte, *Dissert.*, Berlin, 1888; Zambianchi, *Gaz. d. Osp.*, 1888, ix, 93; Mattison, *Quart. Jour. Inebr.*, 1888, x, 57; *Med. and Surg. Reporter*, 1891, lxx, 645; Mannheim, *Ztschr. f. klin. Med.*, 1890, xvi, 380; Falck, *Therap. Monatsh.*, 1890, iv, 511 and 564; Viau, *Odontologie*, 1893, xiii, 97; Scott, *Australas. Med. Gaz.*, 1895, xiv, 94; Fox, *New England Med. Monthly*, 1896, xv, 197; Benedict, *Internat. Med. Mag.*, 1898, vii, 514; Black, *Med. Era*, 1908, xvii, 508; Gibson, *Lancet*, 1910, i, 568; Yawyer, *New York Med. Jour.*, 1910, xcii, 1132; de Vasconcellos, *Tribuna med.*, 1911, xvii, 153; Gottheil, *Jour. Cutan. Dis.*, 1912, xxx, 1; Henley, *Dominion Dent. Jour.*, 1913, xxxv, 162; Bose, *Brit. Med. Jour.*, 1913, i, 16; Hewitt, *Rep. Brit. Assoc. Adv. Sci.*, 1913, 238; Guillain, *Jour. méd. Franc.*, 1914, viii, 235; Aitken, *South African Med. Rec.*, 1915, xiii, 29; *Bonjour, Rev. méd. de la Suisse Rom.*, 1920, xl, 368; Sabatucci, *Policlinico, Med. Sect.*, 1922, xxix, 235.

A 4 per cent. solution of cocain was freely applied to the face of a young woman who was treated for facial blemish. The patient walked to the window and fell dead.

Forty minims (2.5 c.c.) of a 4 per cent. solution of cocain (about $1\frac{1}{2}$ grains—0.097 gm.—of the alkaloid) were injected into the seat of a rectal fistula of a man of twenty-six years. In three minutes he became unconscious and convulsed, and one minute later died.¹

CASE 4.—Half a grain (0.032 gm.) of cocain was injected into the gum. The patient, a woman, became wildly delirious, the pupils were dilated, the extremities cold, the respirations hurried and irregular. Treatment by injections of brandy and ether into the rectum was followed by recovery.²

CASE 5.—One grain (0.065 gm.) was injected into an external hemorrhoid which was to be removed. The pulse became indistinguishable, the heart-beats 40 a minute, the hands and arms in a strong clonic spasm, the extremities cold, the pupils widely dilated, and the urine suppressed. Patient recovered.³

CASE 6.—Twenty drops of a 6 per cent. solution of cocain (about $1\frac{1}{2}$ grains—0.078 gm.—of the alkaloid) were given a man hypodermically. There was sudden collapse, with great dilatation of the pupils, quickened breathing, irregular pulse of 160, symptoms from which the patient recovered.⁴

CASE 7.—A man took $4\frac{1}{2}$ grains (0.312 gm.) of cocain hydrochlorid. Symptoms: failure of eyesight, loss of use of the legs—appeared like a drunken man—cramps in the abdomen, pulse from 80 to 86, profuse sweating. Recovery followed in six days.⁵

CASE 8.—A man of twenty-four years took 8 or 9 grains (over 0.5 gm.) of cocain hydrochlorid. The symptoms included numbness in the mouth, tongue, and throat, extending later to the stomach and abdomen, also muscular movements resembling those of a bad case of chorea, the movements, however, being slower and more regular. Treatment: nitrite of amyl, calomel, castor oil. Recovery.

CASE 9.—A man suffering from disease of kidneys took 20 grains (1.3 gm.) of cocain and died an hour after. At the autopsy the lungs were found congested, as were the brain and the underlying part of the stomach. There was a blood-clot in the heart. It was inferred that death occurred from paralysis of both the cardiac and respiratory centers.⁶

CASE 10.—A girl of sixteen years took about 10 grains (0.64 gm.) of cocain in 10 per cent. solution on an empty stomach and then drank hot tea. Death occurred in forty minutes.⁷

CASE 11.—A girl of seventeen years took from 12 to 15 grains (almost 1 gm.) of cocain and died in forty minutes. At the autopsy the pupils were found dilated, the heart valves normal, with a small quantity of dark, fluid blood in the right ventricle, the left ventricle being empty, the lungs congested and highly crepitant, the brain anemic but its meninges engorged, the liver, spleen, and kidneys hyperemic, the bladder containing 3 or 4 ounces of urine.⁸

CASE 12.—A girl took a teaspoonful of cocain in a glass of beer and died in great pain half an hour after. At the autopsy the brain, pons, and medulla were found engorged, and there was red serum in the side ventricles. The liver, kidneys, and spleen were congested. The stomach contained dark red mucus, yielding plain chemical tests for cocain.⁹

CASE 13.—Patient received a hypodermic injection of 20 minims of a 2 per cent. solution of cocain hydrochlorid prior to operation. In two or three minutes he became nervous with heightened reflexes, accelerated pulse and deepened respirations; flashes before eyes; vertigo; shooting pains in arms, legs, and face. In about ten minutes became nauseated and vomited. All symptoms gradually increased for about one hour. Pulse then 120; respirations deep and slow; reflexes greatly increased; clonic spasms of all muscles of legs, arms, and inferior maxillary; marked accentuation of ideas; hands cold; skin dry; pupils moderately dilated; mouth and tongue dry; no loss of consciousness. Recovery.¹⁰

¹ J. B. Mattison, Dublin Jour. Med. Sci., 1895, xcix, 116.

² C. E. Gooding, Lancet, London, 1888, i, 394.

³ J. Miller, New York Med. Jour., 1894, lx, 660.

⁴ N. Teeter, Therap. Gaz., 1895, xix, 11.

⁵ C. S. Kilhman, Lancet, London, 1887, i, 17.

⁶ Editorial, Fletcher Case, Lancet, 1889, i, 292.

⁷ G. M. Johnston, Brit. Med. Jour., 1895, ii, 1162.

⁸ O. H. Garland, Lancet, London, 1895, ii, 1104.

⁹ Fagerlund, Vrtlschr. f. ger. Med., 1894, 3 f., viii, Suppl., 94.

¹⁰ Lodge, Dental Summary, 1912, xxxii, 44.

CASE 14.—Sailor returned from shore-leave apparently in good condition, although face appeared flushed and he seemed nervous and uneasy. He walked forward on the main deck, suddenly ran to side and jumped overboard, starting to swim away from ship. Picked up by boat crew, but resisted rescue. Symptoms on examination were severe retching and vomiting; extreme nervousness with jactitation; muscular spasms and general rigidity of muscles; head retracted; pupils widely dilated; pulse somewhat rapid but of good volume; later became small and feeble. Subject soon passed into a stupor from which he recovered in a short time. Later investigation showed that this man had been "snuffing" cocain while on shore.¹

CASE 15.—The patient, a man forty-six years of age, complained of pain in the lower right quadrant of abdomen. On the preceding day he suffered from "colic" and vomited three times. Temperature 100° F., pulse 96, respirations 24. Patient entered hospital and the appendix was removed. That night at 12 p. m. the resident physician attempted twice to catheterize the patient, but without success. Slight bleeding followed each attempt. About two hours later "3 drams of a 4 per cent. cocain solution were injected into the urethra. The patient immediately had a convulsion and died." The amount of cocain given was approximately 0.5 gram. Postmortem examination showed dilatation of the heart, acute congestion of the organs, and edema of the meninges.²

Postmortem Appearances.—There are no postmortem findings which are at all characteristic of cocain poisoning. The liver, kidneys, spleen, lungs, brain, and meninges are markedly congested, while the mucous membrane of the stomach may show slight hyperemia (see Cases 9, 11, 12, and 15).

Tests.—Cocain is both a methyl- and a benzoyl-ester of ecgonin, and therefore yields to hydrolysis or saponification, giving first methyl-alcohol and then benzoic acid. With this well-ascertained structure, however, no delicate and distinctive chemical tests have as yet been elaborated for cocain. Reliance may best be placed upon: (1) Biologic tests; (2) the test for benzoic acid; (3) the crystalline form of the gold and platinum chlorids; (4) Seiter's modification of Giesel's test; (5) Metzger's test.

Biologic Tests.—For these a neutral solution of a salt of the alkaloid is employed. Brought by a glass rod into contact with the tongue or lip, repeating the contact upon the same spot, cocain gives a sense of numbness and a characteristic insensibility to touch. (If not too dilute, there is a slight bitterness of taste.) With full effect there is a blanching of the color of the mucous membrane. The cessation of sensation lasts but a few minutes unless the application be repeated. A solution of 4 per cent. causes both numbness and blanching in marked degree. The strength of a solution obtained in analysis should be judged by comparison with graded solutions of known strength of cocain upon the same subject. Upon the eye the anesthetic and blanching effects upon the conjunctiva are obtained, and an additional test, that of dilatation of the pupil; this effect is not so extreme as that of atropin, and much less persistent. If injected hypodermically solutions of cocain produce anesthesia at the point of application.

Chemical Tests.—While many chemical tests have been advocated for the detection of cocain, few of them are sufficiently delicate for use with the small amounts of material with which one works in toxicologic

¹ Bloedorn, U. S. Naval Med. Bull., 1913, vii, 415.

² Kellert, Jour. Lab. and Clin. Med., 1918, iv, 129.

examinations. However, the following are of special value as identification tests:

1. **The Test for Benzoic Acid.**—Unless made with drop quantities and the use of a magnifier, this test must fail from lack of delicacy in ordinary analysis for poisons left in the body after death. To a well-concentrated, clear, aqueous solution—which need not exceed 1 drop—on a glass slide, add about one-tenth its volume of concentrated sulphuric acid, and heat the liquid on the water-bath for about five minutes. Add concentrated ammonia from a capillary pipet nearly to neutralization, making sure, by a minute slip of litmus-paper, that the reaction is not alkaline. Now add from the capillary tube a very little ferric chlorid solution. A buff-colored precipitate should be obtained if cocain was present in sufficient quantity in the liquid taken. Ferric benzoate is not soluble in very dilute acetic acid. The slide may be placed alternately over white and black ground, under the magnifier, in

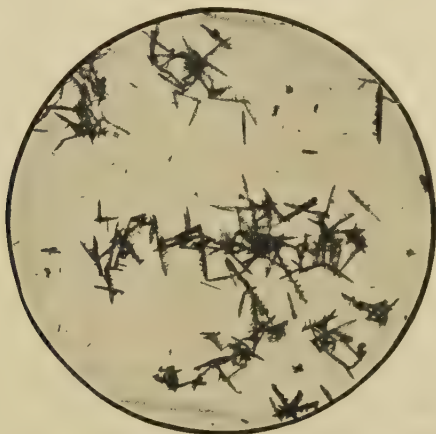


FIG. 48.—Cocain with gold chlorid.

judging of the result. A control test should be made. This test is, of course, far from characteristic as it is given by most of the cocain substitutes and, also, by any compound liberating benzoic acid on heating with acids.

Guerbet's Test for Benzoic Acid.¹—To 0.1 mg. or more of the alkaloidal residue, obtained in the extraction processes, add 3 to 4 drops of fuming nitric acid and evaporate to dryness. Take up the mixed nitro compounds with 1 drop of a 10 per cent. solution of stannous chlorid, heat for two or three minutes, cool and add 2 drops of a 1 per cent. solution of sodium nitrite and 3 or 4 drops of a 1 per cent. solution of β -naphthol in 10 per cent. ammonium hydroxid. A deep orange-red precipitate is formed in the presence of benzoic acid. If this precipitate be dried and dissolved in 1 c.c. of concentrated sulphuric acid a violet red solution is obtained which, on pouring into water, changes

¹ Jour. pharm. et de chim., 1920, xxii, 321.

to a brilliant orange yellow color, still visible with 0.01 mg. of benzoic acid.

2. **The Gold Chlorid Test.**—A solution of cocain hydrochlorid, which may be prepared by careful treatment of a film of residue of the free alkaloid with a drop or two of very dilute hydrochloric acid, is at once precipitated by auric chlorid when the alkaloidal solution is as strong as 1 : 3000. Under the microscope stellate crystals are discerned resembling fern-fronds and melting at 198° C. (388.4° F.). Denigès¹ advocates a microchemical application of this test. In solutions of 1 : 12,000 the crystals are obtained. The test should be conducted on the scale indicated in the preceding paragraph, and if the precipitate be amorphous it should be warmed, and then, if necessary, diluted, to obtain the crystals upon gradual cooling.

3. **The Platinum Chlorid Test.**—If a few drops of an aqueous solution of platinum chlorid be added to the solution of cocain hydrochlorid, a yellow precipitate is formed, which appears, under the microscope, as large feathers sometimes arranged in stellate form.² If the solution be more dilute (such as 1 : 600) most of the crystals "resemble carpet tacks, consisting of short, well-formed prisms with a single branch from the center."

4. **Seiter's Modification of Giesel's Test.**—According to Giesel,³ if an aqueous solution of cocain hydrochlorid (containing about 0.01 gm.) be treated with 1 c.c. of 3 per cent. potassium permanganate solution, a purple-violet crystalline precipitate of cocain permanganate is produced, the supernatant liquid assuming a purple-violet tint. Lyon⁴ recommends the use of a $n/10$ normal solution of potassium permanganate. This precipitate is formed instantly but is unstable, decomposing in a few hours, leaving a brown hydrated manganese dioxid. However, if examined under the microscope when first precipitated, the crystals appear as translucent, violet red, rhombic (nearly rectangular) plates often grouped to form rosettes. If the solution be dilute the crystals form only on evaporation.⁵

Seiter⁶ has modified this reaction so that it becomes of great value in toxicologic work, giving positive results in dilutions of 1 : 3000. To 1 c.c. of an aqueous cocain solution, obtained in the extraction processes, add 1 drop of 25 per cent. sulphuric acid and 1 c.c. of saturated permanganate solution. After standing some time a drop of the liquid is removed to a slide, the cover-glass adjusted, excess of liquid removed, and a drop of water drawn under the cover-glass by means of a piece of filter-paper placed on the opposite edge. Examine the slide under the microscope, when the characteristic violet-red rectangular plates of cocain permanganate appear.

¹ Ann. chim. anal. chim. appl., 1919, i, 65.

² See Lyon, Amer. Jour. Pharm., 1888, lvii, 10.

³ Pharm. Zeit., 1886, xxxi, 132; Chem. Centralbl., 1887, 1448.

⁴ Amer. Jour. Pharm., 1886, lviii, 240.

⁵ See Allen, Commercial Organic Analysis, 4th ed., 1912, vi, 324.

⁶ Amer. Jour. Pharm., 1911, 83, 265; also Seiter and Enger, Ibid., 195; see Hankin, Analyst, 1911, xxxvi, 2.

5. Metzger's Test.—On adding a few drops of a 5 per cent. solution of chromium trioxid (chromic acid) or a 7.5 per cent. solution of potassium dichromate to an aqueous solution of cocain hydrochlorid, a yellow precipitate is produced which redissolves on shaking the mixture. On now adding concentrated hydrochloric acid a permanent orange-colored crystalline precipitate of fine needles is formed and the solution remains yellow for several days. This reaction is shown in solutions of 1 : 1000 and is not duplicated, according to Metzger, by any of the other common alkaloids.¹

Separation from Animal Tissues.—The method of extraction directed for atropin (p. 463) is suitable for cocain. Instead of chloroform as an immiscible solvent, benzene may be employed.

As stated above cocain is quite readily saponified, so that failure to detect the alkaloid in certain cases has been attributed to such decomposition by the tissues of the body. It has been claimed, and apparently corroborated by experimental work, that administration of cocain by mouth or hypodermically is not followed by its elimination in the urine to any appreciable extent.² The decomposition of cocain in the living body was, therefore, assumed to occur rapidly and fairly completely, although ecgonin was not found in the urine. It was, however, shown³ that this decomposition did not progress so rapidly after death in presence of putrefying material, although Proells⁴ states that he was able to detect cocain in cadaveric material at most after fourteen days; while Sonnie-Moret⁵ asserts that toxicologic examination will give negative results unless cocain be taken in considerable quantities.

Recent experiments by Rifätwachdani⁶ indicate that even prolonged contact with living tissue does not, apparently, cause destruction of cocain. He shows that a large percentage of the intake is excreted by the urine as such, and that in any period of frequent administration of cocain, a tendency toward cumulative manifestations may arise, but the proportionate daily output in the urine increases with the use of the alkaloid. His report also outlines a method for detection of ecgonin in the urine, satisfactory proof of the elimination of which had not been previously advanced.

Cocain Substitutes.—A large number of synthetic products have been introduced as local anesthetics and substitutes for cocain in the attempt to obtain a more stable product having the local effects of cocain, but without its toxic power. Although most of these do have a lower degree of toxicity, yet practically all of them produce, in cer-

¹ *Pharm. Zeit.*, 1889, xxxiv, 697. For other tests see Denigès, *Bull. soc. pharm.*, Bordeaux, 1914, lii, 385; Pisani, *Rend. soc. chim. ital.*, 1914, vi, 132; *Pharm. Jour.*, 1914, xciii, 589.

² See Wiechowski, *Arch. f. exper. Path. und Pharmakol.*, 1901, xlv, 155; Kohlhardt, *Arch. f. klin. Chir.*, 1902, lxiv, 927; Fischer, *Dissert.*, Berlin, 1903; Mussi, *L'Orosi*, 1881, xi, 270; Kleine, *Ztschr. f. Hyg.*, 1901, xxxvi, 1.

³ See Vitali, *Manuale di chim. toss.*, 1893, 403; Glasenap, *Dissert.*, St. Petersburg, 1894.

⁴ *Apotheker-Zeitung*, 1901, xvi, 779 and 788.

⁵ *Chem. Centralbl.*, 1893, 1, 859; *Jour. de pharm. et de chim.*, 1893, xxviii, 390.

⁶ *Biochem. Ztschr.*, 1913, liv, 83; see also Gröde, *Arch. f. exp. Path. und Pharmakol.*, 1912, lxvii, 172; Kuroda, *Jour. Pharm. and Exper. Therap.*, 1915, vii, 423.

tain cases, untoward symptoms, while many of them have caused death. These substitutes react, in a general way, like alkaloids, yielding precipitates with most of the alkaloidal reagents, yet their isolation and detection in cases of poisoning is not as yet extensively investigated.

As far as the literature reveals we are unable to find record of a single toxicologic investigation of a case of poisoning by any of these substitutes, as the history in the fatal cases has usually been sufficiently clear to permit of a determination of the cause of death. "They owe their origin to the discovery that the local anesthetic action of cocain is due to the radical of benzoic acid in combination with a nitrogen-containing basic group. The simplest of these compounds, *anesthesin*,¹ *propäsin*,² and *cycloform*, are respectively, ethyl, propyl, and isobutyl esters of para-amino benzoic acid ($C_6H_4NH_2COOH$); *orthoform*³ and *orthoform-new* are the methyl esters of oxy-amino-benzoic acids ($C_6H_3OHNH_2COOH$). All of these are too weak or too insoluble in water to be useful for hypodermic injections; they are used as local applications." They may be regarded as non-toxic.⁴

Besides the above cocain substitutes, others of a somewhat more complex structure and, at the same time, more soluble and more toxic, have from time to time, found more or less use in medical practice. However, α -eucain⁵ ($C_{19}H_{27}NO_4$) and *holocain* ($C_{18}H_{22}N_2O_2$) are too toxic for general use, the latter being several times as toxic as cocain; while *stovain*⁶ ($C_{14}H_{21}NO_2$), *alypin*⁷ ($C_{16}H_{26}NO_2$), and *tropacocain*⁸ ($C_{15}H_{19}NO_2$) have not proved entirely satisfactory. For our purposes, therefore, this discussion narrows down to β -eucain and novocain. Practically all of these substitutes differ from cocain in dilating the vessels or, at least, in not constricting them as does cocain. Hence, it is customary to employ adrenalin (epinephrin) in conjunction with them.

β -Eucain Hydrochlorid.—The base, β -eucain itself, is not employed as a local anesthetic. The official hydrochlorid and the non-official lactate are quite frequently used. The hydrochlorid is a syn-

¹ Ritsert, Pharm. Zeitung, 1907, xlvii, 356.

² Stürmer and Lüders, Deutsch. med. Wehnschr., 1908, xxxiv, 2310.

³ Goulier et Guinard, Compt. rend. Soc. de biol., 1898, v, 802 and 883; Audibert, Compt. rend. Soc. d'obs., de gyn., etc., 1904, vi, 110; Schmidt, Montreal Med. Jour., 1906, xxxv, 189.

⁴ See New and Non-official Remedies, 1916, 28.

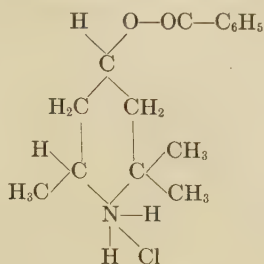
⁵ Neuhaus, Monatsh. f. prakt. Dermat., 1903, xxxvii, 166; Coroner's report of McCormac Case, Pharm. Jour., 1907, xxv, 321.

⁶ Fourneau, Compt. rend. Acad. de sc., 1904, cxxxviii, 766; Jour. de Pharm. et de Chim., 1904, xx, 481; Launay et Billon, Compt. rend. Acad. de sc., 1904, cxxxviii, 1360; Delattre, Thèse, Paris, 1905; Baylac, Compt. rend. Soc. de biol., 1906, lx, 254; Piquand et Dreyfus, Ibid., 1907, lxiii, 411; Coroner's report, Pharm. Jour., 1908, xxvii, 819; Orтали, Gazz. d. osp., 1911, xxxii, 1067; Smith and Hatcher, Jour. Pharm. and exper. Therap., 1917, ix, 231.

⁷ Impens, Deutsch. med. Wehnschr., 1905, xxxi, 1154; Jacobs, Calif. State Jour. Med., 1917, xv, 268.

⁸ Giesel, Pharm. Zeitung, 1891, xxxvi, 419, isolated this derivative from Java coca leaves; see also Liebermann, Ber. d. d. chem. Gesellsch., 1891, xxiv, 374, 2336 and 2587; 1892, xxv, 927, for a discussion of the synthesis of this compound; Chadbourne, Brit. Med. Jour., 1892, i, 402, shows that it is less toxic than cocain and has more marked anesthetic properties.

thetic derivative of 2, 6, 6-trimethyl-4 benzoyl-oxypiperidin with the molecular formula of $C_{15}H_{21}NO_2HCl$, and the graphic structure.



This salt occurs as a white crystalline powder; odorless; permanent in the air. One gram is soluble in 30 mls. of water, 35 mls. of alcohol, and 6 mls. of chloroform at 25°C . (77°F .); it is more soluble in boiling water and boiling alcohol. The aqueous solution is neutral to litmus, and¹ may be sterilized by boiling without decomposition. On the addition of alkali hydroxids or carbonates to the aqueous solution the free base is precipitated, which is soluble in ether. Ammonia water produces a precipitate which redissolves, but is reprecipitated on addition of more ammonia. In the course of a toxicologic examination, the free alkaloid is obtained by shaking the alkaline fluid with ether.

The saturated aqueous solution gives a white curdy precipitate on addition of a few drops of mercuric chlorid solution. While this reaction was supposed to distinguish β -eucain from α -eucain and cocain, Eigel¹ has shown that all three of these basic substances are precipitated, when in saturated solution, by mercuric chlorid, but if the reaction be carried out by adding 1 drop (or a multiple) of a 5 per cent. solution of mercuric chlorid to the same quantity of a 1 per cent. solution of α -eucain, β -eucain, and of cocain, the α -compound and cocain are thrown down as a white precipitate, while the β derivative is not precipitated. β -Eucain yields no color reactions with sulphuric or nitric acids, but gives an orange-yellow precipitate with Dragendorff's reagent, a lemon-yellow precipitate with Hager's reagent, and a white precipitate with Sonnenschein's reagent. It is distinguished from cocain by the character of the gold chlorid and platinum chlorid precipitates, the former yielding with β -eucain an amorphous precipitate and the latter a crystalline deposit of leaves, cubes, and rosettes, both of which precipitates are quite distinct from those produced with cocain. If the questionable residue, obtained in the extraction processes, be treated in a porcelain dish with 10 drops of concentrated sulphuric acid and then with a small particle of potassium iodat, β -eucain gives a brown, olive green with blue and violet streaks, and finally a dirty violet color; while cocain, under the same treatment, gives the same coloration, but novocain gives a brown color. If a portion of the residue be dissolved in very dilute hydrochloric acid and treated with a very small amount of a solution of potassium permanganate a

¹ Apoth. Ztg., 1903, xviii, 603.

violet color is produced with cocain which remains for some time, while with β -eucain a rapid decolorization of the permanganate solution occurs with separation of manganese. On the addition of a dilute (3 per cent.) solution of chromic acid to about 5 c.c. of a 1 per cent. solution of the residue, cocain shows, with the first drop, a yellow precipitate which dissolves on shaking and reappears on the addition of hydrochloric acid; while with β -eucain the yellow precipitate formed dissolves in hydrochloric acid.¹ The picrate of cocain melts at 165° to 166° C. (329° to 330.8° F.), while that of β -eucain melts at 230° C. (446° F.).

β -Eucain has been widely used in surgical practice as a local anesthetic, and is much less toxic than cocain (3.75 times less, according to Marcinowski). It has, however, produced very marked symptoms in some cases from small doses (0.01 gm.), while in others much larger amounts have been injected with no untoward results. The general symptomatology of this toxic action may be noted from the following cases.

CASE 1.—A male received by lumbar injection 0.01 gram of β -eucain hydrochlorid. Sudden lumbar pains; nausea; vomiting; dyspnea; precordial pains; motor unrest and marked headache, which lasted eight days.²

CASE 2.—Man, forty years of age, received an urethral injection of 10 c.c. of a 2 per cent. solution of β -eucain hydrochlorid (3 gr.) to permit of operation. Patient passed through operation with no special symptoms. On next day was given the same dosage. Almost immediately showed marked psychic disturbance with delusions; very uneasy; gesticulated wildly; speech incoherent, although patient was fully conscious; pulse 100; respirations rapid and gasping; spastic contractions of muscles of arm, leg, and face. Treatment: wine, camphor, stimulation with faradic current, inhalations of oxygen. Recovery.³

CASE 3.—Young healthy soldier received an injection of "rather less than 2 grains" of β -eucain, together with a few drops of adrenalin, into the body and root of penis. In short time patient became quiet and pale and complained of feeling faint. Limbs began to twitch, while the little finger of the right hand became tightly clenched. Respiration became slow and labored; pulse-rate was increased; pupils contracted about to pin-point size. He became very cyanotic, respiration almost ceased, and soon lost consciousness. Treatment: artificial respiration and strychnin. Recovery.⁴

CASE 4.—Farmer, age sixty, admitted to hospital for operation. Twenty minutes before operation received $\frac{1}{4}$ grain of morphin followed with 3 ounces of 0.25 per cent. (3.4 gr.) solution of β -eucain hydrochlorid. During the operation patient began to perspire freely and complained of being tired. On leaving operating table he was perspiring profusely and skin was clammy; respirations occasionally sighing; pulse 88 and weak. Skin over entire body cold and clammy; pupils contracted; pain in head and abdomen. One hour later it was impossible to feel pulse; respirations of Cheyne-Stokes type. Treatment: epinephrin solution and $\frac{1}{100}$ grain of atropin, 1 liter of saline intravenously. Recovery from poisoning, but patient died from embolus on fifth day.⁵

¹ Parsons, Chem. Centralbl., 1902, i, 478.

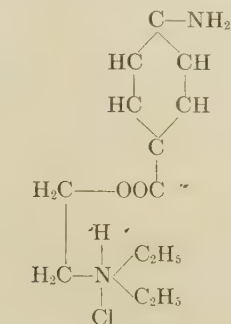
² Engelmann, Münch. med. Wehnschr., 1900, xlvii, 1531.

³ Kraus, Deutsch. med. Wehnschr., 1906, xxxii, 67.

⁴ Way, Jour. Royal Army Med. Corps, 1914, xxiii, 209.

⁵ Orr, Jour. Amer. Med. Assoc., 1916, lxvi, 1857. For further cases see Lohmann, Therap. Monatsh., 1897, xi, 427; Dolbeau, Contribution à l'étude de l'anesthésie en chirurgie oculaire par l'emploi de l'eucain B, Paris, G. Carre et C. Naud, 1897; Vinci, Virchow's Arch., 1897, cxlix, 217; Ibid., 1898, cliv, 549; Braun, Samml. klin. Vorträge, 1898, No. 228; Heinze, Virchow's Arch., 1898, clii, 466; Legueu et Kendirjy, Presse méd., 1900, ii, 299; Jackson, Lancet, 1900, i, 928; Gessner, Jour. Amer. Med. Assoc., 1900, xxxiv, 668; Parsons, Jour. Amer. Chem. Soc., 1901, xxiii, 885; Marcinowski, Deutsch. Ztschr. f. Chir., 1902, lxx, 417; Simon, Münch. med. Wehnschr., 1904, li, 1287.

Novocain (Procain).—The free base is not used in medical practice, the hydrochlorid and, to a less extent, the nitrate being employed as local anesthetics. The hydrochlorid is a synthetic derivative of 1-para-amino-benzoyl, 2-diethylamino ethane, with the molecular formula $C_{13}H_{20}N_2O_2$, and the following graphic structure.



Novocain hydrochlorid

This salt crystallizes from alcohol in fine colorless needles which melt at 156° C. (312.8° F.). It is soluble in an equal weight of water, but requires 30 parts of alcohol for solution. The aqueous solution is neutral and may be boiled without decomposition. The novocain nitrate occurs in small, colorless, and odorless crystals, which are soluble in water and alcohol and melt at 100° to 102° C. (212° to 215.6° F.). From the aqueous solution of either of these salts alkali hydroxids and carbonates (not, however, the bicarbonates) precipitate the free base, novocain, in the form of a colorless oil, which soon congeals to a crystalline mass. This base crystallizes from dilute alcohol with 2 molecules of water and melts at 51° C. (123.8° F.); while from ether or ligroin it separates out in the form of anhydrous shining prisms, which melt at 58° to 60° C. (136.4° to 140° F.). Solutions of these salts give precipitates, even when dilute, with the general alkaloidal reagents.

In the course of a toxicologic examination, novocain is obtained by shaking the alkaline fluid with ether, just as are cocain and β -eucain. As this substance contains the amino group it responds to the color reaction for such bodies, thereby differing from both cocain and β -eucain. This reaction is as follows: To a portion of the residue add a little dilute hydrochloric acid followed by a few drops of potassium nitrite solution. On alkalinizing this mixture with sodium hydrate solution and treating with a few drops of an alkaline solution of β -naphthol, a cherry-red color with a slight tinge of blue appears. As novocain contains ethyl groups, which are easily split off, the odor of iodoform may be obtained by dissolving in sodium hydrate solution the precipitate produced by a solution of iodine in potassium iodid and warming slightly, a reaction which is not given by cocain or β -eucain. Most of the other differentiating reactions are of pharmaceutic rather than of forensic interest, so will be omitted.

Novocain hydrochlorid and nitrate are local anesthetics similar

in action to cocain, but are non-irritant and less toxic than cocain, and the other cocain substitutes. While they exert prompt local action, the effect is not sustained unless a simultaneous injection of adrenalin be made. Eggleston and Hatcher¹ have shown that novocain (or as they style it procain, according to the nomenclature of the Council of Pharmacy and Chemistry of the A. M. A.) has a toxic action, considerably less than that of cocain, it requiring 40 to 45 mg. per kilo for a fatal dose when injected intravenously into cats. Although used in doses of 1 to 4 grains (0.1 to 0.25 gm.), yet these salts have produced toxic symptoms with the smaller dose in many cases and, at least, 6 deaths. The toxic symptomatology may be noted from the following cases:

CASE 1.—Man, age forty-one, received, prior to operation, an injection of 3 c.c. of distilled water containing 1 mg. of strychnin hydrochlorid and 1 dg. of novocain between the eleventh and twelfth dorsal vertebrae. Onset of anesthesia was rapid, reaching 3 inches above level of nipples in fifteen minutes. One-half hour after receiving the injection, the patient complained of difficulty of breathing and attempted to vomit. This was followed by rapid cessation of respiration, the muscles of the arms becoming rigid from spasm. Death followed quickly in spite of vigorous treatment.²

CASE 2.—Man, age forty-three, received a hypodermic injection of 2 drams of a 1 per cent. solution of novocain (a little more than 1 grain) containing not more than $\frac{3}{4}$ minim of a 1 : 1000 solution of adrenalin hydrochlorid. The injection was made slowly during a period of three minutes. Patient was quiet during the injection, but without the slightest warning pupils became widely dilated and fixed; complete loss of consciousness; cold clammy sweat on face; respiration and pulse slow, the former shallow and scarcely audible, while the latter was thready and irregular; rigidity of whole body. Recovery was almost as sudden as the induction of the symptoms.³

COLCHICUM AND ITS ALKALOID, COLCHICIN

General Description.—*Colchicum autumnale*, the meadow saffron, owes its poisonous effects chiefly to the alkaloid colchicin, the distinctive chemical constituent of the plant. The closely related alkaloid, colchicein, seems to be much less active than colchicin, Paschkis⁴ asserting that it is almost inert. Colchicein is present in very small amount in the plant. Zeisel⁵ maintaining that it is split off from colchicin during the process of extraction. The drug is an

¹ Jour. Pharm. and Exper. Therap., 1919, xiii, 433; Jour. Amer. Med. Assoc., 1919, lxxiii, 125; see also Roth, Bull. 109, Hyg. Lab. U. S. P. H., 1916; Jour. Pharm. and Exper. Therap., 1917, ix, 352; Jour. Nat. Den. Assoc., 1918, iv, 129.

² Gabbett, Indian Med. Gaz., 1910, xlv, 54.

³ Bogg, Lancet, 1913, i, 561. For other cases see Braun, Deutsch. med. Wehnschr., 1905, xxxi, 1667; Biberfeld, Med. Klin., 1905, i, 1218; Heineke and Laewen, Deutsch. Ztschr. f. Chir., 1906, lxxx, 180; Liebel, Münch. med. Wehnschr., 1906, liii, 201; Le Brocq, Brit. Med. Jour., 1909, i, 783; Petrow, Zentralbl. f. Chir., 1909, xxxvi, 482; Kehr, Arch. f. klin. Chir., 1909, lxxxix, 97; Deutsch. Monatsschr. f. Zahnheilkde., 1910, xxxviii, 48; Frankfurter and Hirschfeld, Arch. Anat. u. Physiol., 1910, 515; Piquand and Dreyfuss, Jour. de Physiol. et de Path. Gén., 1910, xii, 70; Coffart, Rev. de Stomatol., 1911, xviii, 107; Goodinge and Etheridge, Brit. Med. Jour., 1912, ii, 1607; Schlesinger, Med. Klin., 1912, viii, 1236; Braun, Ergeb. der Chir. u. Orthop., 1912, iv, 1; Giffen and Gundrum, Calif. State Med. Jour., 1914, xii, 415; Amerigo, Rev. de med. y cirug. pract., 1915, cvii, 220; Morian, Zentralbl. f. Chir., 1915, xxviii, 493; Scandola, Gaz. d. Osp., 1915, xxxvi, 50; Merusel, cited by Scandola; Siegel, Med. Klin., 1916, xii, 34; Hatcher and Eggleston, Jour. Pharm. and Exper. Therap., 1916, viii, 385; Doubleday, Guy's Hosp. Gaz., 1919, xxxiii, 144.

⁴ Med. Jahrb., 1883, 257; 1888, 569.

⁵ Monatsh. f. Chemie, 1886, vii, 585.

importation into the United States from plants collected in the temperate regions of Europe and northern Africa, being known to the ancients as a poison and as a remedy.

Colchicin is present in all parts of the plant, but chiefly in the seeds¹ and corm (root), both of which serve as the basis of the pharmacopœial preparations, the extract being derived from the root, while the fluid-extract and tincture are prepared from the seed. The wine of colchicum is no longer official. According to the U. S. Pharmacopœia, ninth revision, the dried root should yield not less than 0.35 per cent. of colchicin; the dried seeds not less than 0.45 per cent.; the extract not less than 1.25 nor more than 1.55 per cent.; the fluidextract not less than 0.36 nor more than 0.44 per cent., and the tincture not less than 0.036 nor more than 0.044 per cent. The pure alkaloid, colchicin, is official.

Symptoms of Poisoning by Colchicum.—The symptoms resemble those of an irritant, such as arsenic or a bacterial toxin, with purging, vomiting, and depression. The particular responses of the body to the irritative attack show wide variation in different cases. Among the symptoms in the majority of the cases are a burning sensation in the throat, nausea, vomiting, severe colicky pains, great thirst, frequent purging, various derangements of the urinary excretion (especially anuria and hematuria), coldness and moisture of the skin, and prostration of strength. Pulse is small and irregular, later becoming imperceptible. Respiration gradually becomes shallow, death being due to paralysis of respiratory center. Blood picture may show a leukocytosis with myelocytes and even nucleated red cells. On repeated injections a basophilia may result.² The mind is not directly affected, although there may be some confusion or even delirium, vertigo, depression, apathy, and collapse following. The irritation of the mucous membrane is a physiologic rather than a local effect of the poison, so that it results from hypodermic injection. The somewhat gradual development of the poisoning is explained by the statement that the alkaloid is not poisonous until, by oxidation, it is resolved into oxydicolchicin³ ($C_{22}H_{25}NO_6$)₂O.

Period When Fatal.—The symptoms usually come on within from one to three hours after the poison has been taken, the amount ingested having but little influence on the duration of this preliminary stage.⁴ In the majority of fatal cases from a single dose death has taken place in about twenty-four hours. It has been delayed for several days or even weeks. The excretion of this poison is very slow, so that in repeated doses it may be cumulative (Kobert).

Fatal Quantity.—Of the pure alkaloid, colchicin, $\frac{1}{3}$ grain (0.02 gm.) is liable to cause death, 4 reports of death from even $\frac{1}{20}$ grain being reported in periods ranging from twelve hours to ten days.⁵

¹ See Blau, *Ztschr. f. österr. Apoth.-Verein*, 1903, xlii, 187.

² See Dixon and Malden, *Jour. of Physiol.*, 1908, xxxvii, 50.

³ Jacobi, *Arch. f. exp. Path. und Pharmacol.*, 1890, xxvii, 119.

⁴ See Mairat et Combenale, *Compt. rend. Acad. de sc.*, 1887, civ, 439 and 515.

⁵ See Klin.-Ther. Wehnschr., 1900, vii, 407; also Courtois-Suffit et Trastour, *Bull. et mém. Soc. des hôp. de Paris*, 1903, xx, 254.

By analogy with fatal effect on dogs 1 grain (0.065 gm.) would be fatal for a man (Kobert); $\frac{1}{12}$ grain (0.005 gm.) has caused violent diarrhea. The fatal quantity of colchicum or its preparations may be estimated from these data, with recognition of the wide variation in strength of the drug, as already stated.

Treatment.—The stomach, as well as large intestine, should be washed out as soon as possible with water containing tannic acid; the mucous irritation may be allayed by mucilaginous drinks and



FIG. 49.—Meadow-saffron or colchicum (*Colchicum autumnale*).

opiates; the abdominal pains relieved by hot fomentations. Hypodermics of strychnin and atropin are useful for the collapse, the respiratory failure being further treated by artificial respiration. It is not probable that an appreciable extent of saponification of the alkaloid (as referred to below) can be accomplished by an antidote in the body.

Statistics.—Cases of poisoning by colchicum have been numerous. The literature reveals 9 cases of poisoning with colchicin, 7 of which were fatal. Of 132 reports of poisoning with preparations of colchicum, 118 were accidental, 6 suicidal, and 8 homicidal. Of these 8 homicidal

cases, the most interesting is that of Catherine Wilson, who was tried in 1862 for the murder of 4 persons with colchicum seeds placed in wine or brandy.¹ In the accidental poisoning with colchicum, leaves have been eaten by mistake for salad, while the seeds have been eaten by children. A large number of cases of poisoning in Rome, characterized by gastro-intestinal irritation, were attributed by Ratti² to the use of milk from goats whose pasturage contained colchicum plants. Schottelius³ attempted to prove that feeding animals with large amounts of leaves and seeds of colchicum would poison the milk, but was unsuccessful.

CASES OF POISONING BY COLCHICUM

CASE 1.—Wine of colchicum of the strength of 4 ounces (113 gm.) of the seeds to a pint (576 c.c.) was taken by mistake by 17 persons, each taking from 3 to 11 ounces (89 to 325.2 c.c.). The persons were from twelve to forty-five years of age. The symptoms of poisoning began in from forty-five to ninety minutes, and consisted of vomiting and bilious discharges. The purging was delayed in the cases of those who took the smaller quantities. There were severe cramps, irritation in the throat, hoarseness, intense thirst, small pulse, and slight dilatation of the pupils. Consciousness was retained, as was the muscular strength, with sleeplessness. Seven of the patients died in from nineteen to twenty-nine hours after the poison was taken, and 10 recovered. Of the latter, 1 had taken 11 ounces (325.2 c.c.) of the wine.⁴

CASE 2.—Five patients in a hospital in Toulon, France, were each given by mistake 2 ounces (57 c.c.) of wine of colchicum. The earliest symptoms appeared in about two hours. There were burning pains in the stomach, nausea and continued vomiting, abundant purging, a pale and cold surface, a small pulse, great thirst, and somewhat later than the first symptoms a sense of burning in the throat. There was tenesmus, both rectal and vesical. There was no loss of motor, sensory, or mental power. The 5 cases were all fatal in from nineteen to twenty-six hours. In the *postmortem* appearances there was no trace of inflammation in the throat or esophagus, the mucous surface of the stomach and intestines was softened and red, the stomach was distended with liquid, and the liver and spleen were congested. No colchicin was found in the vomited matters.⁵

CASE 3.—A woman fifty-six years of age took 1 ounce (30 c.c.) of the wine of colchicum in divided doses in the course of twelve hours. There were nausea, vomiting, slight purging, heat and pain in the throat, pain in the stomach, thirst, a cold moist skin, and a feeble pulse. The symptoms continued for three days, when the patient recovered.⁶

CASE 4.—A woman of twenty-two years took a poisonous quantity of colchicum. There were severe chills, purging, abdominal pains, and vomiting. Death ensued thirty-six hours thereafter. The stomach was found enlarged, the kidneys congested, the brain and heart hyperemic. Analysis of the contents of the stomach revealed no colchicin.⁷

CASE 5.—On February 7th a man aged forty-three years took 0.003 gram (about $\frac{1}{30}$ gr.) of colchicin in divided doses over a period of one hour. Entered hospital on February 12th, having suffered from gastro-intestinal disturbances in the intermediate period. At this time he was much depressed, mind clear, extremities cold, no abdominal pain, but tenderness on pressure, tremors. On the two succeeding days patient continued to pass bloody material from mouth, the stools containing bright red blood. Urine showed blood and albumin. On February 15th the depression increased, the patient being semiconscious, ecchymotic spots on limbs,

¹ See Taylor, Principles and Practice of Med. Jurisp., 6th ed., 1910, ii, 703.

² Pharm. Jour. and Tr., 1875, vi, 47.

³ Cited by Kobert, Intoxikationen, 1906, ii, 581; see, however, Barrat et Remlinger, Rec. de méd. vét., 1911, lxxxviii, 617.

⁴ Major, Med. Times and Gaz., London, 1874, 1, 275.

⁵ M. Roux, L'Union Méd., March 27, 1855, ix, 145; Lancet, London, 1855, i, 474.

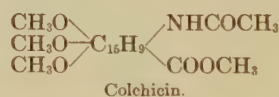
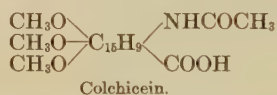
⁶ Kennard, Amer. Jour. Med. Sci., 1857, lix, 69.

⁷ Moyer, Med. News, 1894, lxiv, 457.

no headache, no abdominal pain, stools not fetid or diarrheal in character. Slight improvement on next day, but death occurred on February 17th, the tenth day after taking the colchicin.¹

Postmortem Appearances.—The findings at autopsy are not characteristic of colchicin poisoning. The alimentary tract shows all the evidences of acute gastro-enteritis, with numerous hemorrhagic areas especially in the upper part of the bowel, although mild cases may reveal nothing more than simple catarrhal inflammation of the duodenum. The kidneys may show marked congestion and, occasionally, evidence of a toxic nephritis. The heart muscle may be hyperemic. In some cases the pupils may be dilated, due, no doubt, to the asphyxia. Blood may be dark red in color.

Chemical Properties and Tests.—Colchicin is the methyl-ester of a nitrogenous base (or amid), colchicein. It is very unstable, being decomposed (saponified) on heating with very dilute acids or alkalies into colchicein and methyl alcohol. If the heating be continued longer the colchicein is converted into trimethyl-colchiceinic acid and acetic acid, the former being still further split into dimethyl-colchiceinic acid and then into colchiceinic acid. Further study of these saponification products by Zeisel² has shown that colchicein contains three methoxyl groups, although the basic group remaining ($C_{15}H_9$) is not as yet identified. The nitrogen of these alkaloids is probably in an acid amid group, certainly not combined as in the pyridin derivatives.³ Chemically speaking colchicein is, so far as our knowledge extends, acetyl-trimethyl-colchiceinic acid, with the formula $C_{21}H_{23}NO_6$; while colchicin is the methyl ester of this acid, with the formula $C_{22}H_{25}NO_6$. Graphically, they may be represented as follows:



Colchicin ($C_{22}H_{25}NO_6$) occurs in pale-yellow amorphous scales or as a pale-yellow amorphous powder, turning darker on exposure to light; odorless or, if moist and slightly warmed, having an odor resembling hay. It melts between 142° and 146° C. (287.6° and 294.8° F.); 1 gram of colchicin dissolves in 22 mls. of water, 220 mls. of ether, 100 mls. of benzene at 25° C. (77° F.); also in 21 mls. of water at 80° C. (176° F.); freely soluble in alcohol, chloroform, and amyl alcohol; insoluble in petroleum ether. Its aqueous solution is intensely bitter and is neutral in reaction to litmus, is levorotatory, and of a yellow color. Besides the above official form of colchicin it is found, when

¹ Courtois-Suffit et Trastour, Bull et mém. Soc. méd. des hôp. de Paris, 1903, xx, 254. For other cases of colchicum or colchicin poisoning see Sprega, Gazz. d. osp., 1890, xi, 626; von Meydell, St. Petersburg. med. Wehnschr., 1881, vi, 166; Klin.-Ther. Wehnschr., 1900, vii, 407, cited by Kobert; Benedict, Internat. Med. Gaz., 1898, vii, 514; Musterle, Münch. tierärztl. Wehnschr., 1909, liii, p. 292; Maurel, Compt. rend. Soc. de biol., 1909, lxxvii, 687.

² Monatsh. f. Chemie, 1883, iv, 162; 1886, vii, 557; 1888, ix, 1 and 865; see also Gordin and Prescott, Proc. Amer. Pharm. Assoc., 1900, xlviii, 135.

³ See Windaus, Sitzungsber. der Heidelberger Akad. der Wissenschaft, 1910.

crystallized from chloroform, as yellow prismatic needles,¹ containing 2 molecules of chloroform of crystallization ($C_{22}H_{25}NO_6 \cdot 2CHCl_3$). On boiling this form with water, amorphous colchicin separates. As its basic characters are very feebly marked, colchicin is extracted by suitable immiscible solvents (such as chloroform and amyl alcohol) from both acid and alkaline solutions. Colchicin is precipitated from its aqueous solutions by most of the alkaloidal reagents, although not by some. Thus, tannic acid, Marmé's, Sonnenschein's, Wagner's, Dragendorff's reagents yield prompt precipitates with the neutral solution, while Mayer's reagent reacts only in acid solutions. Platinum chlorid and picric acid yield no precipitates with colchicin, while gold chlorid slowly throws down colchicin from its acidified solution in the form of a yellow amorphous, changing to crystalline, precipitate soluble in alcohol.

Colchicein ($C_{21}H_{23}NO_6 + \frac{1}{2}H_2O$), when crystallized from water, forms lustrous white needles, melting at 139° to 141° C. (282.2° to 285.8° F.); when anhydrous it melts at 172° C. (341.6° F.). It is very slightly soluble in cold water, more readily in hot water; dissolves easily in alcohol, chloroform, and amyl alcohol; almost insoluble in absolute ether and benzene. Soluble, as is colchicin, in mineral acids, alkalis, ammonia and alkali carbonates, forming yellow solutions. Its aqueous solutions possess both acid and feebly basic properties and are levorotatory. With many of the alkaloidal reagents it yields precipitates which are indistinguishable from those with colchicin. Lead and copper acetates produce in aqueous solutions of colchicein a white or yellowish-green precipitate respectively.²

Chemical Tests.—1. **Nitric Acid Reaction.**—Colchicin treated with concentrated nitric acid gives a violet-red color, changing to green and then to yellow. On addition of strong potassium hydroxid solution, the color is changed to red. Colchicein and oxydicolchicin also give this reaction.

2. **Sulphuric Acid Reaction.**—If a trace of colchicin (0.05 mg.) be treated with concentrated sulphuric acid an intensely yellow (lemon) color is produced. If now a drop of concentrated nitric acid be added a play of colors is observed, the yellow changing to greenish-yellow, green, bluish-green, wine-red, and finally light yellow. If strong potassium hydroxid solution be added to this yellow solution, the color is changed to red.

3. **Ferric Chlorid Reactions.**—If a few drops of ferric chlorid solution be added to an aqueous solution of pure colchicin, no color is produced, but on heating a brownish-red color is developed, which changes to brownish black. Colchicein does not give this reaction, although oxydicolchicin does.

If a few drops of ferric chlorid solution be added to an alcoholic solution of colchicin a garnet-red color is produced at once.

¹ See Houde et Labord, *Le Colchique et la Colchicine*, Paris, 1887; also Merck, *Apoth. Ztg.*, 1916, referred *Chem. Drug.*, 1916, lxxxviii, 40.

² For a discussion of the properties of these two alkaloids see Schmidt, *Pflanzenalkaloide*, in *Biochemisches Handlexikon*, 1911, v, 354 et seq.; also Barger, in *Allen's Commercial Organic Analysis*, 4th ed., 1913, vii, 4 et seq.; Tunmann, *Apoth. Ztg.*, 1918, xxxiii, 443, 447, 454; *Chem. Zentralbl.*, 1919, xi, 42.

If a few drops of ferric chlorid solution be added to a hydrochloric acid solution of colchicin, a green color is produced in a short time. If this solution be boiled it becomes greenish black and cloudy. On now shaking this greenish solution with chloroform, the latter reagent settles out appearing garnet-red or brown in color, if at least 2 mg. of colchicin be present; if less be present, the chloroform is yellowish (Zeisel's reaction).

Colchicein is colored green with ferric chlorid when in aqueous solution, thus differing from pure colchicin.

4. **Barillot's Test.**—A small amount ($\frac{1}{10}$ mg.) of the free alkaloid, in the form of an ether or chloroform residue, is intimately mixed with 1 c.c. of concentrated sulphuric acid and 0.25 gram of oxalic acid. This golden-yellow mixture is sealed up in a small glass tube and heated to 120° C. (248° F.) for one hour, when the tube is opened and its dark reddish-brown contents diluted with water. An excess of alcoholic sodium hydroxid is now added, followed by an excess of acetic acid, when a yellow precipitate is formed. Extract this mixture with chloroform, draw off this solvent and evaporate it to dryness, when a yellow residue is obtained, which becomes violet-red on treatment with concentrated nitric acid and raspberry red with concentrated sulphuric acid. This reaction is especially valuable in differentiating colchicin from morphin and codein, both of which yield blue colorations; and from ptomains, which give no similar results.¹

Biologic Tests.—The effects produced by injection of colchicin into animals are not sufficiently characteristic to warrant absolute conclusions. Great difference is observed in the sensitiveness of various animals to colchicin, quantities usually in question in toxicologic cases being insufficient for such experiments. It has been shown that the rabbit requires a dose of 7 mg. per kilo; a cat $\frac{1}{2}$ to 1 mg. per kilo, and a dog 1 to 5 mg. per kilo to produce death. The frog shows great tolerance to colchicin, requiring from 100 mg. to 1 gram to prove fatal. Fühner has found that the frog may be rendered much more sensitive to colchicin by placing the animal in an incubator for a few days before injecting. Such animals are killed in two to five days by doses of $\frac{1}{10}$ to 1 mg. This peculiarity of the reaction of colchicin with frogs at room and incubator temperature serves to distinguish this poison from others, with which it might be confused, as no other known poison shows increased effect when given to a warmed frog.

The best animal for forensic tests of colchicin is the white mouse. This animal is killed by a dose of $\frac{1}{20}$ to $\frac{1}{5}$ mg. of colchicin, the symptoms appearing in about twenty-four hours and progressing slowly. The slow onset and progress of the toxic action is characteristic of colchicin.²

Separation from Animal Tissues.—In a toxicologic examination

¹ Bull. Soc. Chim., 1894, 3 Ser., xi, 514.

² See Jacobi, Arch. f. exp. Path. und Pharmakol., 1890, xxvii, 125; Maurel, Compt. rend. Soc. de biol., 1909, lxxvii, 687; Fühner, Arch. f. exp. Path. und Pharmakol., 1910, lxxiii, 357; Nachweis und Bestimmung von Giften auf biologischem Wege, Berlin, 1911, 76, 149.

for colchicin, it must be remembered that this alkaloid is readily saponified by heating with dilute acids or alkalis. The extraction process must, therefore, be conducted with extreme caution, using room temperature or, at least, one not over 50° C. (122° F.). A further point to bear in mind is that colchicin and oxydicolchicin are extracted from both acid and alkaline mixtures by chloroform and amyl alcohol, but not by petroleum ether. Colchicein is extracted from acid solutions by benzol.

To purify the yellowish amorphous product, which is usually yielded by the extraction processes, the method of Autenrieth¹ is very serviceable. Extract the yellowish residue with warm water. Filter the solution, and when cold extract it first with petroleum ether to remove fatty and resinous matter and follow this with chloroform. Or, preferably, precipitate the colchicin from its aqueous solution with tannic acid. Collect this precipitate upon a filter and wash with cold water. Mix the moist precipitate with freshly precipitated and washed lead hydroxid. Dry this mixture, grind to a powder, and extract with chloroform. Evaporation of the solvent leaves nearly pure colchicin.

The urine, kidneys, and intestines are most likely to yield colchicin in postmortem analysis, as this alkaloid is excreted through the bowels and, in part, as colchicein through the kidneys. Colchicin resists decomposition for a long period in presence of putrefying material, so that it should be capable of detection several months after death (two hundred and fifty-eight days in 1 case).²

Colchicin-like Ptomaines.—In any toxicologic examination the possible presence of basic putrefactive products must be borne in mind. It is to be emphasized, however, that the reactions of these ptomaines, so far as the literature reveals, do not agree in all points with those of the alkaloid which they simulate, so that careful comparative tests and insistence upon identical color or precipitation reactions and biologic tests should prevent mistaken identity.

In a few medicolegal cases the tests for colchicin have been brought into question. While it is true that these tests may be simulated by basic putrefactive products, yet no ptomaines so far discovered have given reactions similar in every detail to those mentioned above. The following cases are cited in point.

Liebermann³ obtained from a cadaver a product which passed into ether from acid as well as from alkaline liquids and which was yellow and amorphous. The aqueous extract had no specially marked taste. While it resembled colchicin in certain respects, it differed in giving white precipitates with chlorin water, with mercuric chlorid, and with mercuric potassium iodid; in giving a reddish-violet color after standing with sulphuric acid and in failing to give the nitric acid reaction. In this connection it may be recalled that Ogier⁴ asserts that ptomaines never give the characteristic violet color with nitric acid.

¹ Detection of Poisons, 4th ed., 1915, 65.

² See Obolonski, Vrtljschr. f. ger. Med., 1888, xlv, 105; Ogier, Ann. d'hyg., 1886, xv, 445; Traité de chim. Tox., 1899, 633; Proels, Apoth.-Zeitung, 1901, xvi, 492.

³ Ber. d. d. chem. Gesellsch., 1876, ix, 151.

⁴ Traité de chim. Tox., 1899, 636.

In a case of suspected poisoning Baunert¹ examined the tissues twenty-two months after death and found a substance that gave many of the reactions of colchicin. It was extracted from acid solutions with ether, to which it imparted a yellow color. On evaporation of the ether a yellow amorphous substance remained which was soluble in water with yellow coloration. It could also be extracted from acid solution by chloroform, benzene, and amyl alcohol, but not by petroleum ether. It was not so easily removed from alkaline solutions. On evaporation there remained a feebly alkaline residue having a markedly bitter taste and being devoid of crystalline form. With phosphomolybdic acid, phosphotungstic acid, potassium bismuth iodid, potassium mercuric iodid, iodine in potassium iodid, tannic acid, and gold chlorid this substance gave the same reactions that were obtained by parallel experiments with genuine colchicin. Concentrated sulphuric and dilute nitric and hydrochloric acids dissolved it, forming yellow solutions. Strong nitric acid colored the substance dirty red, scarcely to be called a violet. When this body was purified as much as possible the coloration with strong nitric acid became a beautiful carmin red. The addition of water changed the red into yellow, and caustic soda produced a dark, dirty orange. It differed from colchicin in giving precipitates with picric acid and platinum chlorid and in not responding to the ferric chlorid test of Zeisel. Later Brieger examined this putrefactive body and found it to be a peptone-like substance, which was completely inert when tested biologically.

In a medicolegal investigation² (*Affaire R*), Brouardel, Ogier, and Pouchet apparently isolated a basic compound which fully agreed with colchicin in all reactions, the symptoms and postmortem findings also indicating this poison. Schutzenberger and Vulpian, testifying for the defendant, claimed to have isolated from 2 cadavers in which the possibility of poisoning by colchicin was precluded a basic substance which coincided in its reactions with the base isolated from the suspected organs, showing reactions which were very similar though not identical with colchicin. In view of these findings, the experts for the prosecution would go no further than to state, "Symptoms, autopsy, and chemical analysis are in accord with the view that death resulted from colchicin, but we would not affirm scientifically, with absolute certitude, that this hypothesis was correct." It would seem, therefore, that the analyst should, in all cases, be especially guarded in his conclusions as to the cause of death in toxicologic investigations, yet a study of the above reported cases will show that the reputed reactions obtained with the putrefactive products were, in reality, not those of colchicin. In this connection it may be recalled that certain products have been isolated from beer, which show quite as much similarity to the colchicin reactions as do putrefactive basic products.³

¹ Arch. der Pharm., 1887, ccxxv, 911; Lehrb. der gerichtl. Chem., 1907, i, 406.

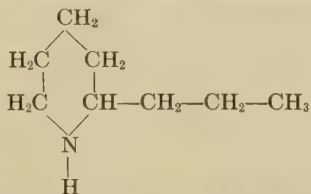
² Ann. d'hyg., 1886, xv, 230.

³ See Dannenberg, Arch. d. Pharm., 1876, ccviii, 411; van Geldern, Ibid., 1876, ccix, 32; Tjaden-Moddermann, Ztschr. f. anal. Chem., 1877, xvi, 328.

CONIIN AND POISON HEMLOCK

General Description and Relations.—*Conium maculatum*, common or spotted "poison" hemlock, is a plant naturalized from Europe, growing wild along roadsides and in waste places in the United States. Its toxic properties were known to the ancients, who used it as a judicial poison, Socrates among others being put to death by drinking its infusion.¹ Conium and its preparations are no longer official in the United States. This plant contains six alkaloids, d-coniin (the characteristic poisonous alkaloid), methylconiin, conhydrin, pseudoconhydrin, γ -conicein, and ethylpiperidin.

d-Coniin ($C_8H_{17}N$) exists in all parts of the plant, being most abundant in the fruit, the proportion increasing with the maturity of the seed. The fruit should yield at least 0.5 per cent. of coniin by assay. Coniin was first isolated by Giesëcké² and is of special historic interest, as it was the first alkaloid to be synthesized. This synthetic coniin, as first reported, agrees in all its properties with the natural alkaloid except that it is optically inactive.³ In later work Ladenburg⁴ showed that synthetic coniin was really isoconiin, which could be converted into d-coniin by heating to 300° C. (572° F.). His newer method of synthesis is slightly different from his original technic, the d-isoconiin differing from the natural d-coniin only in its degree of rotation. Structurally speaking, d-coniin is the simplest of the alkaloids, being known chemically as α -n-propylpiperidin and represented by the formula—



d-Coniin, when pure, is a colorless, almost odorless, dextrorotatory, oily fluid, but soon becomes yellow and, after long standing, resinous, and acquires a peculiar, penetrating, characteristic odor described as "mousy." This odor is especially noticeable when coniin is diluted with water. It is strongly alkaline in reaction, neutralizing acids perfectly. It is somewhat volatile at ordinary temperatures and distills with alcohol or water, being found in the distillate from alkaline solutions in the systematic search for poisons. At higher temperatures it distills unchanged in an atmosphere of hydrogen, but undergoes slight decomposition in presence of air. It boils at approximately 166° C. (330.8° F.). Its specific gravity at 20° C. (68° F.) is 0.844, while its specific rotation is $[\alpha]_D = +15.7^\circ$ at 19° C. (68.2° F.). In the cold coniin solidifies to a crystalline mass, which becomes fluid at

¹ See Imbert-Gourbeyre, *De la mort de Socrate*, Paris, 1875; Lewin, *Die Gifte in der Weltgeschichte*, Berlin, 1920, 67.

² *Arch. der Pharm.*, 1827, xx, 97.

³ Ladenburg, *Ber. d. d. chem. Gesellsch.*, 1884, xvii, 772, 1121, 1676; 1885, xviii, 47, 913, 1587, 2961; 1886, xix, 2578.

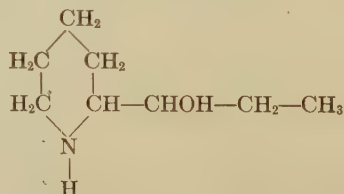
⁴ *Ber. d. d. chem. Gesellsch.*, 1906, xxxix, 2486.

—2° C. (28.4° F.). It is soluble in 90 parts of water, less soluble in hot water, the cold saturated solution becoming turbid on heating. It is readily soluble in alcohol, ether, ethyl acetate, chloroform, petroleum ether, benzene, and acetone. It is readily removed from aqueous or alkaline solutions by the above immiscible solvents and, to a slight extent, from slightly acid solutions by ether.

d-Coniin readily forms salts, which are colorless and odorless, and are soluble in water, alcohol, and chloroform, but not in petroleum ether. On adding a fixed alkali to these salts the peculiar "mousy" odor is developed. The hydrochlorid crystallizes from its aqueous solution in large rhombic crystals, which melt at 220° C. (428° F.). The platinum chlorid salt, $(C_8H_{17}NHCl)_2PtCl_4$, separates at first as an oil, but soon crystallizes in orange-yellow crystals which melt at 175° C. (347° F.) when anhydrous, and crystallize from hot alcohol as deep red four-sided plates. The gold salt $(C_8H_{17}NHClAuCl_3)$ precipitates as an oil, but on standing for a few days forms crystals which melt at 77° C. (170.6 F.). The solutions of the hydrochlorid form crystalline precipitates with phosphotungstic and phosphomolybdic acids, with picronic acid, and cadmium-potassium iodid, while with the other alkaloidal reagents the precipitates, if any, are amorphous.¹

Methyl-coniin ($C_9H_{19}N$) is a derivative of coniin in which the H atom attached to N is replaced by methyl. It is, therefore, n-methyl- α -n-propylpiperidin. It was first discovered in 1854 by Planta and Kekulé in conium, but was isolated in a pure state by Wolffenstein,² and previously, synthesized by Passon.³ It is a colorless, alkaline, volatile, oily liquid with an odor similar to that of coniin, but more amine-like. It boils at 174° to 176° C. (345.2° to 348.8° F.) and has a specific gravity of 0.8318 at 24.3° C. (75.74° F.), at which temperature its specific rotation is $[\alpha]_D = +81.33^\circ$. A levorotatory form of methyl-coniin is also known, but this is not found in conium. The hydrochlorid of d-methyl-coniin is a white crystalline salt melting at 188° to 189° C. (370.4° to 372.2° F.).

Conhydrin ($C_8H_{17}NO$) is a derivative of coniin in which the H atom of the α -ethyl group is replaced by hydroxyl (OH). It is, therefore, α -ethyl-piperidyl-alkin, with the structure—



It was discovered by Wertheim⁴ in conium, and is found in commercial coniin. It forms colorless, glittering, double-refracting plates,

¹ See Dilling, *Pharm. Jour.*, 1909, 4, ser. xxix, 34, 70, 102.

² *Ber. d. d. chem. Gesellsch.*, 1894, xxvii, 2614.

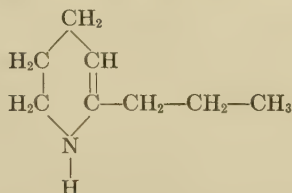
³ *Ibid.*, 1891, xxiv, 1678.

⁴ *Ann. der Chem. und Pharm.*, 1856, c, 329; 1862, cxxiii, 157; 1863, cxxvii, 75; 1864, cxxx, 269.

which react alkaline, melt at 120.6° C. (249° F.), and boil at 226° C. (438.8° F.) without decomposition; its odor resembles that of coniin. It is dextrorotatory, and is soluble at 15° C. (59° F.) in 25.6 parts of water, in 5.8 parts of alcohol, in 66 parts of ether, and in 5.2 parts of chloroform.

Pseudoconhydrin ($C_8H_{17}NO$) is possibly stereo-isomeric¹ with conhydrin, although Löffler² believes these bases to be simply structurally isomeric. This base was first discovered by Merck in conium and investigated by Ladenburg and Adam.³ It crystallizes from ether in fine white thread-like crystals, which melt between 105° and 106° C. (221° and 222.8° F.), and boil between 236° and 236.5° C. (456.8° and 457.7° F.). It is alkaline in reaction and is dextrorotatory, $[\alpha]_D = +10.98^{\circ}$. The preparation of the hydrochlorid serves to purify this base and to separate it from the associated conhydrin, as the hydrochlorid of conhydrin liquefies in air quickly and is easily soluble in alcohol, while the salt of pseudoconhydrin is permanent in air and is difficultly soluble in absolute alcohol.⁴

γ -Conicein ($C_8H_{15}N$) is one of 5 isomeric coniceins, but this gamma derivative is the one present in conium and commercial coniin, in which it may be found to the extent of 70 per cent.⁵ This basic substance may be derived from coniin by oxidation of 2 H. atoms, the gamma compound being the α -n-propyl-tetra-hydropyridin with the following structure:



It is a colorless liquid, turning dark with age, and has an odor resembling coniin. It distills with steam and boils at 171° to 172° C. (339.8° to 341.6° F.). It is optically inactive and has a specific gravity of 0.8724 at 15° C. (59° F.). It is slightly soluble in water, has a strong alkaline reaction, and a sharp, burning taste. It forms a characteristic crystalline salt with stannic chlorid, which melts at 215° C. (419° F.) with decomposition. It is much more active than coniin, being reported as 12 to 15 times more toxic than coniin.

Symptoms of Poisoning by Coniin.—These vary somewhat, depending, probably, on the amount of γ -conicein present. If the free alkaloid is taken, there is burning sensation in the mouth and throat. The general symptoms are languor and drowsiness, which does not pass into actual sleep, prickling sensations in the muscles, muscular

¹ Engler, Bauer and Kronstein, Ber. d. d. chem. Gesellsch., 1894, xxvii, 1775, 1779.

² Ibid., 1909, xlii, 116.

³ Ibid., 1891, xxiv, 1671.

⁴ See Schmidt, Pflanzenalkaloide in Biochemisches Handlexikon, 1911, v, 20.

⁵ von Hofmann, Ber. d. d. chem. Gesellsch., 1885, xviii, 9, 105.

weakness, pain in head, twitching and tremors together with stiffness and rigidity of some of the muscles. Movements weak and unsteady, gait staggering. Nausea and, occasionally, vomiting with profuse salivation. Speech thick. Deglutition difficult. Respiration at first accelerated and deepened, later becomes slow and labored, weak and irregular, and finally ceases. In most cases there is little disturbance of the intellect, although dulling of special senses may be observed. Pupils somewhat dilated as respiratory failure proceeds, the failure of this function being the cause of death.

Period When Fatal.—The poisonous effect of coniin is very rapid, fatal results being usually reached in one to three hours. So far as the literature reveals, only 3 cases of a longer duration than three hours are known, the case of Bennett¹ in which death occurred in three and a half hours; that of Pepper² in seven hours, and that of Armstrong³ in fifty-two hours.

Fatal Quantity.—The minimum lethal dose of pure coniin is uncertain. Kobert states that about 2 grains (0.13 gm.) of the alkaloid is the lowest fatal dose, and that from $\frac{1}{2}$ to 1 grain (0.03–0.06 gm.) is a seriously poisonous quantity. In the case of Louise Berger death resulted from a dose of 10 to 15 drops (0.42–0.63 gm.), an amount greatly in excess of a fatal dose.⁴ In the experiments by Schroff⁵ upon 27 physicians, 0.003 to 0.085 gram of the pure alkaloid dissolved in alcohol was a toxic dose. As 1 drop of coniin weighs 0.042 gram, it is clear that this would constitute a distinctly poisonous dose.

Treatment.—Evacuation and lavage of the stomach, and then stimulating agents and measures, with every effort to maintain respiration, constitute the treatment. Coniin is excreted rapidly in the urine, so that the effects pass off rapidly if death does not result.

Postmortem Appearances.—These are not characteristic of coniin and are, for the most part, those due to asphyxia. The brain and its meninges show congestion, while the lungs are congested and, at times, edematous. The blood is dark and fluid, becoming brighter red on exposure to air. If the pure alkaloid be taken, the mucous membrane of the esophagus and stomach may show considerable hyperemia, with some ecchymotic areas.

Chemical Tests for Coniin.—1. **General Properties.**—Coniin is an oily liquid with a characteristic “mousy” odor, obtained in full from the base itself, but less markedly from the salts. Its aqueous solution becomes turbid on heating, again clearing on cooling. It is alkaline to litmus and phenolphthalein, differing from nicotine in the fact that its alcoholic solution reddens an alcoholic solution of this latter indicator, while an alcoholic solution of nicotine does not. With aqueous solutions of both coniin and nicotine, phenolphthalein gives

¹ Edinb. Med. and Surg. Jour., 1845, lxiv, 169.

² Med.-Leg. Jour., 1885–86, iii, 179.

³ Trans. Med. Soc. New Jersey, 1880, cxiv, 249.

⁴ Arch. der Pharm., 1861, cvii, 257, 360.

⁵ Cited by Kobert, Intoxicationen, 1906, ii, 1079; see also Tiryakin, Études expérimentelle et clinique sur la conine et ses sels, Thèse de Paris, 1878.

a red color, which disappears on shaking with chloroform in the case of nicotin, but is permanent with coniin.¹ Chlorin water renders an aqueous solution of coniin turbid, while it has no effect on solutions of nicotin. Bromin water produces a crystalline precipitate with coniin and not with nicotin.

2. The vapor of coniin with that of hydrochloric acid produces a white cloud in the air. If a watch-glass is moistened with free coniin, another watch-glass moistened with hydrochloric acid, and the latter glass fitted over the former, the upper glass will receive a deposit of white crystalline, doubly-refracting needles arranged in stellate groups or in dendritic forms or, later, cubical or octahedral crystals of the hydrochlorid of coniin. Similar crystals of the hydrobromid may be obtained by substituting Wormley's reagent for the HCl.

3. Coniin is not colored by concentrated sulphuric or nitric acids, while γ -conicein is colored orange to green. With concentrated sulphuric acid and oxidizing agents, such as vanadic acid, potassium bichromate,² selenic acid, and potassium permanganate, greenish colors are obtained, which change into brown or red on standing or heating.²

4. If coniin be touched with alloxan, a deep purplish-red color is slowly developed, along with white needle-shaped crystals. These treated with caustic potash give a purple color and mousy odor.

5. When coniin is warmed with dilute sulphuric acid and potassium dichromate, butyric acid is formed and, if in sufficient amount, recognized by its odor.

6. **Melzer-Dilling Reactions.**—(a) To 0.5 c.c. of a fairly strong alcoholic solution of the alkaloid add a few drops of carbon disulphid, boil and add excess of water. On now adding a few drops of copper sulphate solution a brown color is produced, which is taken up by ether and yields, on evaporation of the solvent, flat, brown, rhomboid plates with coniin, conhydrin, and pseudoconhydrin. With γ -conicein a brown color is produced but no crystals. Piperidin, itself, yields positive results with this test, but nicotin does not.

(b) To an aqueous solution of the alkaloid add ether and shake thoroughly. Withdraw the ether and evaporate it to dryness. Coniin and γ -conicein remain as fluids, the latter being colored green with concentrated hydrochloric acid. Conhydrin crystallizes in flat plates and pseudoconhydrin in needles.

(c) If uranium nitrate be added instead of the copper sulphate in the test above, and the solution shaken with toluol, this solvent becomes red in the presence of coniin, while it is light yellow or colorless with conhydrin and pseudoconhydrin.

(d) Nessler's reagent produces an amorphous precipitate with aqueous solution of coniin or its hydrochlorid in dilutions of 1 to 10,000, while only a yellow color is produced with the hydrochlorids of con-

¹ Heut, Arch. der Pharm., 1893, ccxxxi, 376.

² For a full discussion of these various color reactions see Dilling, Pharm. Jour., 1909, xxix, 34.

hydrin or pseudoconhydrin.¹ Nicotin does not yield any of the above reactions.

Biologic Test.—The biologic tests on frogs are not especially characteristic, being very similar to those of nicotin, except that much larger amounts are required to produce the results with coniin.

If from 5 to 10 mg. of coniin be injected into the breast lymph-sac of a frog, the animal lies on its back and completely loses its reflexes in fifteen minutes. The beat of the heart is easily visible. If the ischiatic



FIG. 50.—Hemlock (*Conium maculatum*).

nerve be exposed within one to two hours after the injection, no contraction of the foot is seen on electric stimulation, although the muscle itself responds promptly. If such a frog be placed in water and kept till the next day, the electrical excitability of the nerve returns.

If coniin solutions be injected into the musculature of the leg of a

¹ Melzer, Ztschr. f. anal. Chem., 1898, xxxvii, 352 and 357; 1902, xli, 327; Dilling, Pharm. Jour., 1909, xxix, 103. For a method of separation of the conium alkaloids, which is, however, not applicable to toxicologic amounts, see von Braun, Ber. d. d. chem. Gesellsch., 1905, xxxviii, 3108.

frog, the animal becomes limp, dragging the leg when moving. If a muscle preparation of the gastrocnemius be prepared and exposed to the action of coniin, a tonic contraction of the muscle will be observed when the alkaloid is present in amounts of 1 : 2000 to 1 : 5000, while nicotin in strengths of 1 : 100,000 produces even more marked results.¹

For the separation from foods or tissues the process given under Nicotin is to be employed. This alkaloid, however, is of an order of bases so far approaching ptomains and leukomains in constitution that it is not surprising that toxicologists have found it difficult to distinguish coniin from putrefactive products.

Coniin-like Ptomains.—In the examination of cadaveric material for the presence of coniin, it must be remembered that volatile, alkaline, liquid, putrefactive substances, either of endogenous or exogenous origin, may be found, which may simulate coniin to a certain extent. Most of these liquid putrefactive bases have been identified as monamins or as diamins, most of which are extracted by petroleum ether or are found in the distillate from alkaline solution. Some of these diamins, such as cadaverin and putrescin, although open-chain compounds, are derivatives of piperidin and may be converted into piperidin by proper treatment. As these products, as well as derivatives of pyridin, are found in putrefying material, it follows that the positive identification of coniin is extremely difficult and often impossible in the presence of a large amount of decomposing animal tissue. Although the chemical reactions for coniin are not distinctive, many of them being given by piperidin itself, the biologic tests are not shown by ptomains or "cadaveric coniins." It is unfortunate, however, that these latter tests require larger amounts of material than are always at the disposal of the analyst.

For the above reasons, a positive statement that coniin has actually been found must be somewhat guarded. The analyst should insist that the symptomatology and postmortem findings be consistent with coniin poisoning and that the biologic tests be positive, the identity of chemical reactions being simply further confirmation. That confusion has occurred in the past in medicolegal cases and that the reactions of these bodies, although similar in some respects to those of coniin, nevertheless may be differentiated is shown by the following reports:

One of the most celebrated of the trials for murder, in which the presence of coniin in the tissues has been questioned, is the Brandes-Krebs case,² which was tried in Braunschweig in 1874. From the tissues submitted to them two chemists obtained, in addition to arsenic, an alkaloidal substance that they pronounced coniin. The distinguished toxicologist, Otto, was called upon to make a further examination of this substance. He reported that it was neither coniin nor nicotin,

¹ See Fühner, *Nachweis und Bestimmung von Giften auf biologischem Wege*, Berlin, 1911, 87 and 111; Kobert, *Intoxicationen*, 1906, ii, 1081, states that neither nicotin nor coniin-like ptomains produce the typical paralysis after doses of 15 mg. to a frog.

² See Otto, *Anleitung zur Ausmittlung der Gifte*, 6th ed., 1892, 93.

nor any other vegetable alkaloid with which he was acquainted. He converted it into an oxalate, dissolved it in alcohol, evaporated the alcohol, dissolved the residue in water, rendered this solution alkaline with potassium hydroxid, and extracted the base with petroleum ether. On evaporation of this solvent the substance appeared as a bright-yellow oil, with a strong unpleasant odor differing, however, quite markedly from that of coniin. It was strongly alkaline and had an intensely bitter taste. At ordinary temperature it was volatile. From its aqueous solutions it was precipitated by the chlorids of gold, platinum, and mercury. In these reactions it resembled nicotin, but it differed wholly from this alkaloid in the double refractive and crystalline character of its hydrochlorid. With an ethereal solution of iodine, this substance did not give the Roussin test for nicotin, but instead of the long, ruby-red crystals, there appeared small, dark green, needle-shaped crystals. This unknown substance was found to be markedly poisonous. Seven centigrams (1 gr.) injected subcutaneously into a large frog produced instantaneous death, and 44 mg. (0.7 gr.) given to a pigeon caused a similar result.

Brouardel and Boutmy¹ obtained from the body of a woman, who died after suffering with 10 other persons, from choleraic symptoms following the eating of a stuffed goose, a base that gave the odor of coniin, and the same reactions as this base with gold chlorid and with iodine in potassium iodid. The same substance was found in parts of the goose not eaten. It differed from coniin inasmuch as it did not give a red coloration with strong hydrochloric acid, and did not form butyric acid on oxidation. It was poisonous, but in its physiologic action did not resemble coniin.

Selmi² repeatedly found in decomposing animal tissue substances resembling coniin. In one instance he made an alcoholic extract of the tissue and distilled the solution thus obtained. The distillate was acidified with hydrochloric acid and evaporated; the residue was treated with barium hydroxid and ether, the ether being allowed to evaporate spontaneously; he obtained a residue of volatile bases, the greater part of which consisted of trimethylamin. After removing this latter base, the residue had the odor of the urine of mice. In this case there was no possibility of coniin being present in the tissue. In another instance Selmi obtained an unmistakable coniin odor from a chloroform extract of the viscera of a person who had been buried for six months, and in still another instance he obtained a like substance from the tissues of a person who had been buried for ten months.

CASES OF POISONING BY CONIIN AND BY CONIUM MACULATUM

CASE 1.—A man of sixty-five years having suffered for two years from a nervous affection of the facial muscles was directed by his physicians to take 50 minims (3 c.c.) of fluidextract of conium every half hour until he felt the effects, and then to discontinue the medication. The symptoms were recorded as they occurred by the patient's wife at his dictation. This had been his custom in taking medicines

¹ Ann. d'hyg., 1880, 3 S., iv, 352.

² Sulle Ptomaine, 1878, 22.

prescribed by physicians, and at times he had been his own physician. The record so obtained is as follows: "At 4.10 p. m. took 50 minims Squibb's fluidextract of conium. At 4.40 p. m. effect very decided in dizziness, relaxation of muscles and limbs. Fifty minims more then taken. Difficulty of walking immediately, and want of power to control movements. Forced to lie down, but no mitigation of spasms. Limbs and legs weak. Unable to hold head up. Speech thickening some. Pain and heaviness in top and back part of head. Pulse 56. At 5.15 p. m. took 50 drops. Some nausea. Some tremor at the base of the clavicle and in muscles across the chest, just above the sternum. No diminution of spasms about the eyes nor of photophobia. At 5.25 p. m. drowsiness, inclined to sleep. At 5.40 p. m. eyes difficult to open, speech difficult, fulness in throat, prostration nearly complete. Diplopia vastly increased. At 6.10 p. m. nausea, twitchings on right side, trouble to articulate, eyes closed, fulness almost to suffocation in throat. Pulse about 60. In past six —." At this point the patient stopped dictating. He was then seized with nausea, and was unable to vomit. He then wanted electricity applied, but while trying to apply it himself he fell back dead. An autopsy was made about sixty hours after death. In the brain there was venous congestion. The lungs were full of blood. A foreign growth in the brain was found, also certain degenerations of the arteries. Chemical analysis was not made.¹

CASE 2.—A man ate a large quantity of hemlock, believing it to be parsley. He soon afterward lost the power of walking, staggered, and finally fell, but still retained his consciousness and intelligence. In about two hours after taking the poison there was complete paralysis of the upper and lower extremities, with occasional spasmodic movements of the left leg, and the patient had lost the power of sight, deglutition, and speech, but was still sensible. His pulse and breathing were natural. The pupils became fixed, the action of the heart very feeble, and death ensued from paralysis of the muscles of respiration in three and a half hours after the poison had been taken. After death the lungs were found engorged, the heart flabby, the stomach congested, the blood fluid and dark. In the stomach were found the green leaves of the plant in the state of a pulp. Bruised in a mortar with addition of caustic potash, the characteristic mousy odor of coniin was obtained.²

CASE 3.—*Effect of Coniin Upon an Animal.*—A single drop of coniin was placed upon the tongue of a large and healthy cat. In a few seconds the animal was inclined to stand still, and manifested an unsteady gait when disturbed; in two minutes and a half it fell on its right side, then voided urine, had violent convulsive movements of the limbs, and a tremulous motion of all parts of the body. It was dead in three minutes after the poison had been administered. In another experiment the animal, being immediately placed upon its feet, stood perfectly still, and the pupils of the eyes became dilated and insensible; in forty-five seconds the legs of the animal became powerless and it sank upon its abdomen, then passed urine, had violent spasms of the extremities, and died in four minutes after the exhibition of the poison.³

CASE 4.—A soldier having eaten some soup containing hemlock leaves soon fell asleep; in an hour and a half afterward he was insensible and breathed with difficulty; his pulse was slow and hard; the extremities cold; the face bluish and distended with blood, like that of a person strangled. An emetic of tartarized antimony was then administered, but it produced only vain efforts to vomit. He complained of being cold, and soon lost the power of speech and consciousness. He died in about three hours after taking the poison.⁴

CASE 5.—A man twenty-two years of age smelled of coniin contained in a bottle, inhaling deeply. He suffered weakness of the limbs, there were rolling of the eyes, headache, profuse perspiration, and a free flow of the lacrimal fluid before he recovered.⁵

EMETIN AND IPECACUANHA

General Description.—Ipecac is the dried root of *Cephaelis ipecacuanha*, known in commerce as Rio ipecac, or of *Cephaelis acuminata*, known as Cartagena ipecac, yielding not less than 1.75 per cent.

¹ New York Times, April 5, 6, and 13, 1875; Wharton and Stillé's Medical Jurisprudence, 1884, ii, 613; Bell, Tr. Amer. Med. Assoc., 1875, xxvi, 345.

² J. H. Bennett, Edin. Med. and Surg. Jour., July, 1845, 169.

³ Wormley, Micro-Chemistry of Poisons, 2d ed., 1885, 455.

⁴ Haaf in Orfila's Toxicology, 1852, ii, 537.

⁵ H. Schultz, Deutsch. med. Wehnschr., 1887, xiii, 495.

of the ether-soluble alkaloids. The active principle of ipecac was for a long time supposed to be a single alkaloid, emetin, but the work of Paul and Cownley has shown that this principle is made up of three distinct alkaloids, emetin, cephaëlin, and psychotrin, the cephaëlin apparently predominating over emetin in the Cartagena ipecac.

Besides the root, the following preparations of ipecac are official. The fluidextract, of which 100 mils. yield not less than 1.8 nor more than 2.2 grams of the ether-soluble alkaloids of ipecac; the syrup, containing 70 mils. of the fluidextract in 1000 c.c. and yielding not less than 0.126 nor more than 0.154 per cent. of the ether-soluble alkaloids; Pulvis ipecacuanhæ et opii (Dover's powder) containing 10 per cent. each of powdered ipecac and opium; and the hydrochlorid of emetin. The wine of ipecac is no longer official. Ipecac has long been used for its emetic and expectorant virtues, while emetin has found wide application in the treatment of amebic dysentery and, more recently, in oral endamebiasis (pyorrhæa alveolaris).¹

Emetin ($C_{30}H_{44}N_2O_4$) was first prepared by Glenard² and later studied by Paul and Cownley.³ As described by these workers, emetin is a nearly colorless base, which is apparently uncrystallizable. It melts at about 68° C. (154.4° F.), rapidly acquiring a yellowish color on exposure to light. Only slightly soluble in water, but dissolves readily in alcohol, ether, chloroform, and benzene, though only very sparingly in petroleum ether even when hot. On evaporation of any of these solutions, emetin is left as a transparent varnish-like residue, which is strongly alkaline to litmus and neutralizes acids completely. When precipitated from the solutions of one of its salts by alkali hydroxids, emetin is insoluble in excess of the reagents. Emetin is probably a quinolin derivative, being a diacid-tertiary diamine containing 4 methoxyl groups.⁴

Emetin hydrochlorid ($C_{30}H_{44}N_2O_4 \cdot 2HCl$) contains variable amounts of water of crystallization. It occurs as a white or very slightly yellowish crystalline powder, without odor. On exposure to light it gradually darkens. Freely soluble in water and alcohol, its aqueous solution being slightly acid to litmus. Its aqueous solutions yield precipitates with iodine in potassium iodid, with mercuric-potassium iodid, and with platinic chlorid. A 5 per cent. solution of this salt, mixed with potassium bromid or iodid, yields a dense precipitate, which dissolves on the addition of alcohol, this solution giving, when slowly evaporated, tufts of silky needles of the hydrobromid or hydro-iodid.

Cephaëlin ($C_{28}H_{40}N_2O_4$) is apparently a lower homologue of emetin. When precipitated from a solution of one of its salts by ammonia, it is colorless, but rapidly becomes yellow on exposure to light; it melts

¹ See Roger, Brit. Med. Jour., 1912, i, 1424; Ibid., 1912, ii, 405; Bass and Johns, Jour. Amer. Med. Assoc., 1915, lxiv, 553.

² Ann. Chim. Phys., 1876, 5 S., viii, 233.

³ Pharm. Jour., 1893, 3 S., xxiv, 61; Ibid., 1894, 3 S., xxv, 111, 373, and 690; see also Cripps, Ibid., 1895, 4 S., i, 160; Frerichs and Tapis, Arch. der Pharm., 1902, cxi, 390; Karrer, Ber. d. d. chem. Gesellsch., 1916, xlix, 2057.

⁴ See Kunz-Krause, Arch. Scienc. Phys. nat. Geneve, 1895, 3 S., xxxiv, 290; also Barger, Allen's Commercial Organic Analysis, 1913, vii, 37 et seq.

at 102° C. (215.6° F.). By evaporation of a solution in alcohol or ether, the base is left as a faintly yellow transparent varnish-like residue, but in a closed vessel a concentrated ethereal solution gradually deposits bunches of delicate silky needles, which melt at 88° C. (190.4° F.) and, after drying, melt at 119° to 120° C. (246.2° to 248° F.). Cephaëlin is very much less soluble in ether, but more readily soluble in petroleum ether, than emetin, from which it is sharply distinguished by being soluble in alkali hydroxid. The hydrochlorid forms transparent rhombic crystals. While the U. S. Pharmacopœia outlines a test for the presence of cephaëlin in emetin, yet, as Ewe¹ has shown, this test would exclude practically all the emetin on the market. He advocates that an upper limit of 3 per cent. cephaëlin be fixed as the amount of cephaëlin as an impurity in emetin hydrochlorid.

Psychotrin was probably first isolated by Cripps and Whitby² and later by Paul and Cownley.³ It exists in ipecac in small quantities (0.04 to 0.06 per cent.), and has a much higher molecular weight than the other alkaloids of ipecac. It is very sparingly soluble in ether, but readily soluble in chloroform, alcohol, and in alkalis. As obtained by the slow evaporation of its ethereal solution, psychotrin appears as transparent lemon-yellow prisms, which melt at 138° C. (280.4° F.).

Symptoms.—Much depends on the size of the dose, the susceptibility of the individual, and the toxicity of the special commercial preparation used as to the effects of ipecac or emetin. Whether given by mouth, subcutaneously, or intravenously, toxic doses show much the same symptomatology, the effects being manifested in a relatively short time. There is a copious flow of saliva, followed later by nausea and vomiting and considerable abdominal pain; frequent and, ultimately, bloody stools; extreme muscular weakness; vertigo; lethargy; convulsive movements of the muscles; peripheral neuritis; occasionally, anuria or hematuria; expiratory dyspnea; fall in blood-pressure; gradually increasing cardiac weakness, characterized by irregularity accompanied by ventricular fibrillation,⁴ and final diastolic arrest of the heart.

As ordinarily administered in treatment of intestinal or oral endamebiasis, the dosage of $\frac{1}{3}$ grain of emetin hydrochlorid three times daily does not cause such symptoms as the above in all cases. However, it is wise not to continue such a course of treatment longer than ten days, following this with a period without medication of about ten days before a second course is given. Lyon⁵ has found, however, that the oral administration of the above amount is almost always followed by the gastro-intestinal symptoms and urges, therefore, the constant subcutaneous administration of the drug. In a certain number of cases, the continuation of this treatment for several days results in an increase in the number of stools with an increasing weakness and often a delirious

¹ Amer. Jour. Pharm., 1919, xci, 275.

² Year Book Pharm., 1891, 390.

³ Pharm. Jour., 1895, 3 S., xxv, 690.

⁴ See Levy and Rowntree, Arch. Int. Med., 1916, xvii, 420.

⁵ Amer. Jour. Med. Sci., 1915, cl, 97; Thomson and Thomson, Brit. Med. Jour., 1916, i, 881; Mattei, Bull. soc. méd. des hôp. de Paris, 1920, xlv, 531.

toxic condition, leading rarely to death. This points to a cumulative toxic effect of single non-toxic doses.

With pure cephaëlin the symptomatology is much the same as with emetin. The emetic dose of the former alkaloid is, according to Wild,¹ only one-half that of emetin. However, the depression with cephaëlin is less than that of emetic doses of emetin, although the former alkaloid causes a greater fall in blood-pressure and more marked effects upon the kidneys than does emetin.²

Period When Fatal.—Owing to the paucity of reports of death from ipecac or emetin, all that can be said is that death has occurred in one and a half hours after taking a toxic dose of ipecac. The cases of poisoning with emetin, itself, are rather of the chronic or cumulative type, so that death in these cases is a matter of days rather than hours. In Lake's experiments on animals, the range of death was wide, from one to eighteen days. The greater number of the animals die acutely.

Fatal Quantity.—There is considerable divergence of opinion, based upon experimental evidence, as to the lethal dose for animals. This may, possibly, be due to the variation in the toxicity of the different preparations used. Thus, Maurel³ states that the fatal dose for the rabbit is 0.03 gram per kilo. given intravenously, 0.1 gram hypodermically, and 0.15 gram by mouth. Vedder⁴ has found that 2.5 mg. per kilo. intravenously is the minimum lethal dose of emetin hydrochlorid for the rabbit. Ten mg. per kilo. subcutaneously on two successive days is uniformly fatal for white rats. Levy and Rowntree⁵ indicate that dogs show no appreciable reaction to single injections of 10 mg. (1 to 2 mg. per kilo.). Repeated daily injections of this amount cause death in from three to fifteen days; single subcutaneous injections of 30 to 45 mg. (3 to 5 mg. per kilo.) cause the death of the dogs in two to five days; with cats, injections of 2 to 5 mg. per kilo. kill in seven to eleven days; in rabbits, subcutaneous injections of 5 mg. (3 to 4 mg. per kilo.) are uniformly fatal in from five to six days; intravenous administration of emetin hydrochlorid in amounts ranging from 4 to 18 mg. per kilo. in dogs and 6 to 16 mg. per kilo. in cats prove fatal, generally within two days. Lake⁶ believes the acutely fatal dose for rabbits, when given subcutaneously, to be 25 mg. per kilo. Dalimier⁷ establishes as his fatal dose 2 mg. per kilo. by intravenous injection of a rabbit and 3 cg. per kilo. by subcutaneous administration. For the guinea-pig, he believes that 7 mg. per kilo. intravenously and 9 cg. per kilo. subcutaneously are fatal. Applying to man the figures obtained on animals, Dalimier computes the toxic dose for a man weighing 60 kilos. as 0.12

¹ Lancet, 1895, i, 1274.

² See Lewin, Arch. internat. de pharmacodyn. et de therap., 1902, xi, 9; Podwysotszki, Arch. f. exper. Path. u. Pharm., 1879, xi, 231.

³ Compt. rend. soc. de biol. Paris, 1901, liii, 862, 877, 977, 996, and 1125; Ibid., 1902, liv, 10; Bull. gén. de therap., 1902, cxliii, 366; Bull. Acad. de méd., 1914, lxxi, 478; Arch. de méd. exper., 1914, xxvi, 225.

⁴ Jour. Amer. Med. Assoc., 1914, lxii, 501.

⁵ Arch. Int. Med., 1916, xvii, 420.

⁶ Bull. 113, Hyg. Lab., U. S. P. H., 1918, 41.

⁷ Presse méd., 1917, xxv, 33.

gram (1.8 gr.) intravenously and 1.8 gram (27.7 gr.) by subcutaneous injection. These figures are closely in accord with those reported by Spehl and Colard¹ of recovery from 22.2 grains and by Levy and Rowntree of death from 29 grains. According to Dalimier, a total dose of 1 gram of emetin hydrochlorid seems to be about the limit of safety, although Baermann and Heinemann² regard 250 mg. per kilo. as the maximal intravenous dose. Such doses as the latter would, unquestionably, result in quick fatalities. It is wise to remember the possibility of cumulative effects of emetin and stop the drug at the first sign of untoward results.

Treatment.—Prompt discontinuance of the drug. Tannic acid by mouth and per rectum to precipitate the alkaloid present and re-excreted into the bowel. Cardiac stimulants and diuretics. The later effects are treated symptomatically.

Cases of Poisoning by Ipecac or Emetin.—Levy and Rowntree have collected 18 cases of poisoning with emetin, to which are to be added the 2 cases reported by them, the case of Lagane cited by Dalimier, the 2 cases of Johnson and Murphy, and the fatal case of Soca. Only 1 case of ipecac-poisoning was found in the literature.

CASE 1.—A twenty-year-old youth “drank several inches of a bottle of vinum ipecacuanhæ.” One hour after swallowing this dose there was uncontrollable vomiting and a rapid pulse; the extremities became cold and damp with perspiration. Death occurred in an hour and a half. At necropsy there was found subacute congestion of the stomach and first two feet of the intestine. The heart was in diastole. The other organs were normal.³

CASE 2.—Man, age twenty-eight years, suffering with amebic dysentery, received during six days 2 daily hypodermics of 30 mg. of emetin hydrochlorid followed by the dose of 30 mg. three times daily for twelve days, the total amount given being 1.44 grams. At this time the patient showed great lassitude with flaccid paralysis of all muscles, especially of neck. Could not hold head up. Showed difficulty in mastication, swallowing, and articulation. Edema of face. Marked diminution of reflexes, both cutaneous and tendinous. Heart rapid and weak. Volume of urine normal, no albuminuria but diminution of urea and chlorids. Medicine stopped. Improvement began ten days after onset of symptoms. Recovery.⁴

CASE 3.—A man weighing 153 pounds received daily subcutaneous injections of emetin hydrochlorid over a period of twenty days. Average daily dose $1\frac{1}{2}$ grains; total amount 29 grains. A previously existing diarrhea was at first somewhat ameliorated, then markedly intensified. On the sixteenth day of treatment, the patient complained of nausea and abdominal pain. Albuminuria and cylindruria appeared and gradually increased. Finally there was evidence of acute renal insufficiency, with blood in the urine and diminution in the phthalein output, along with an increase in the non-protein nitrogen of the blood. There was marked acidosis. Bronchopneumonia and vasomotor collapse terminated the picture.⁵

CASE 4.—An anemic undernourished woman, weighing 95 pounds, received subcutaneously $\frac{1}{2}$ grain of emetin hydrochlorid daily for four days. An intense diarrhea developed, associated with abdominal pain and tenesmus, which ceased six days after discontinuing the emetin treatment. At the same time she was in a toxic delirious state, which lasted for one week. She recovered rapidly. In this case the daily dose was $\frac{1}{2}$ grain, the total being 2 grains.⁶

¹ Province méd., 1914, xxvii, 176.

² Münch. med. Wehnschr., 1913, lx, 1132 and 1210; see also Pellini and Wallace, Amer. Jour. Med. Sci., 1916, cliii, 325; Van den Branden, Bull. Soc. Path. Exot. de Paris, 1919, xii, 521; Soca, Bull. de la Soc. Méd. des Hôp., 1922, xlvi, 768.

³ Harrison, Lancet, 1908, ii, 536.

⁴ Spehl et Colard, Province méd., 1914, xxvii, 176. Cited by Dalimier.

⁵ Levy and Rowntree, Arch. Int. Med., 1916, xvii, 420.

⁶ Ibid.

CASE 5.—Bricklayer, age twenty-two, admitted to hospital on August 2, 1916 with diarrheal attack, which was proved to be due to infection with the *endameba histolytica*. Condition prior to admission: diarrhea five days prior; onset sudden with cramps and bloody stools; temperature 101° F.; pulse 112; $\frac{1}{2}$ grain doses, twice a day, of emetin hydrochlorid were given from August 10th to 16th. The stools decreased in number during this period, with a morning temperature normal and a slight afternoon rise to 100° F. on two days. On August 21st the stools increased in frequency and continued so for several days with a varying laboratory report from positive to negative for ameba. Emetin hydrochlorid in $\frac{1}{2}$ grain doses, thrice daily, was employed from August 21st to 24th with reduction in number of stools and no effect on pulse-rate. Progress was satisfactory until September 14th, when patient had a chill and fever rose to 101.4° F. with a pulse-rate of 120, and a similar phase on September 17th. Emetin was used from September 5th to 15th and from September 27th to October 3d in $\frac{1}{2}$ grain doses once daily. On October 3d the pulse was rapid; motor weakness and nervousness was marked; blood-pressure 108-64-44. On October 4th, chill followed by temperature of 103° F.; pulse irregular and rapid, the rate being 162; respiration 42; marked dysphagia; bases of both lungs showed evidence of congestion and there was cough with expectoration, the cough being shallow and abortive. Patient died on October 5th. A total of 25 grains of emetin hydrochlorid had been administered. Postmortem findings showed evidence of congestion in bases of both lungs, resembling pneumonic red hepatization; septic bronchitis; stomach and intestines normal.¹

CASE 6.—Patient, age thirty-eight, in United States Army thirteen years and seven months. Entered hospital September 5th. Progressed favorably from admission until October 12th, when he complained of exhaustion and weakness, exhibited extreme motor weakness, characterized by inability to hold the head upright for more than a few seconds and difficulty in swallowing. Inability to raise hands to mouth, and every voluntary effort calls forth a marked, coarse muscular tremor. October 17th, evidence of congestion of the middle and lower lobes of the lung on the right side with marked air hunger and dyspnea. About noon of the same day the patient exhibited signs of extreme cardiac distress, manifested by rapidity, rate 196 and loss of radial pulse. Death on October 18th. This patient had received a total of 23½ grains of emetin hydrochlorid in two courses, with an interval between courses of five days. Postmortem findings: Heart enlarged and fatty, heart in diastole, distention of auricles, engorgement of right ventricle. Upper lobe of lung uniformly congested, as were also entire lower lobes of both right and left lungs. Alimentary tract normal throughout.²

Postmortem Appearances.—The mucous membrane of the stomach and intestines may show marked congestion, indicative of severe gastro-intestinal irritation, although neither of the cases of Johnson and Murphy showed any abnormality. In Levy and Rowntree's case, the large intestine showed "no erosions or ulcerations; the mucous membranes of the rectum was slightly flushed and, microscopically, showed marked infiltration with round cells." The heart is stopped in diastole. Blood clots slowly, the clot being non-retractile. Other organs show no abnormality, although a pneumonia may appear as a terminal infection and give the usual evidences of this disease.

Chemical Tests.—As ordinarily obtained, emetin hydrochlorid

¹ Johnson and Murphy, *Mil. Surg.*, 1917, xl, 58.

² *Ibid.* For other cases see Allen, *Jour. Amer. Med. Assoc.*, 1913, lx, 664; Chauffard, *Presse med.*, 1913, xxi, 521; Lagane, *Ibid.*, 1914, xxii, 465; Eshleman, *New Orleans Med. and Surg. Jour.*, 1914, lxvi, 965; Weis, cited by Eshleman; Lyons, *Amer. Jour. Med. Sci.*, 1915, cl, 97; Hume, cited by Levy and Rowntree; Velazco, *Gaceta Med. de Caracas*, 1916, xxiii, 7. For further discussion of the toxicity of emetin see Zepf, *Arch. internat. de pharmacod. et de therap.*, 1904, xii, 345; Balfour and Pyman, *Jour. Royal Army Med. Corps*, 1916, xxvi, 35; Dale, *Brit. Med. Jour.*, 1915, ii, 895; Guglielmetti, *Prensa Med. Argentina*, 1917, iv, 20; Houssay, *Semana Méd.*, 1917, xxiv, 397; Mery and Mellion, *Compt. rend. soc. de biol.*, 1917, lxxx, 592; Leger et Certain, *Bull. soc. path. exot.*, Paris, 1918, xi, 405; Faroy, *Progrès Méd.*, 1920, xxxv, 454.

frequently contains cephaëlin as an impurity. The chemical tests are, therefore, somewhat indefinite and are, for the most part, given by the combined alkaloids of ipecac rather than by each one separately.

1. If a drop of solution of bleaching powder be applied to a fragment of the residue obtained in the extraction processes and a drop of acetic acid added, a persistent bright orange or lemon-yellow color is produced. If the bleaching powder be added to a solution of the combined alkaloids in dilute hydrochloric acid, an orange color is produced and a yellow precipitate is formed.

2. With the combined alkaloids Fröhde's reagent gives a yellowish-pink coloration, becoming greenish and, on adding hydrochloric acid, changes to greenish blue and then to rose with green at the edges.¹ With pure emetin hydrochlorid Fröhde's reagent gives a bright grass-green color. With pure cephaëlin itself Fröhde's reagent gives no color, although a purple color is shown by some impure specimens, but the hydrochlorid yields an intense blue color.

3. If a few drops of a mixture of potassium ferricyanid and ferric chlorid be added to a hydrochloric acid solution of emetin, a beautiful blue (Prussian-blue) color is produced. This reaction is said to be especially characteristic of the mixed ipecac alkaloids.²

Separation from Tissues.—As these alkaloids are readily extracted from alkaline solution by ether, the process outlined elsewhere for the systematic examination for alkaloids should be followed. The residue should be carefully purified.

ERGOT AND ITS ALKALOIDS

General Description.—**Ergota** (U. S. P.), ergot of rye or spurred rye, is the carefully dried sclerotium (compact mycelium) of the parasitic fungus, *Claviceps purpurea*, replacing the grain of rye (*Secale cereale*). It is also found on other grains as well as on some native grasses of the West. Its official preparations are the extract and fluidextract, while numerous proprietary preparations of the supposed active principles are found on the market.

The chemistry of ergot has been the subject of a large number of investigations, but these have, for the most part, accomplished little beyond introducing confusion as to the active principles. Probably none of the earlier so-called principles were chemically pure, but were rather simply pharmaceutic preparations, the best known of these being ecbolin,³ ergotin,⁴ cornutin,⁵ sphacelinic acid, sphacelotoxin, secalinotoxin,⁶ and chrysotoxin.

¹ See Cripps and Whitby, Year-book Pharm., 1891, 390.

² See Allen and Scott-Smith, Pharm. Jour., 1902, 4 S., xv, 552; Millino, Thèse de Paris, 1917; Mattei, Compt. rend. soc. biol., Paris, 1917, lxxx, 830; Ibid., 1918, lxxxi, 315.

³ Wenzell, Amer. Jour. Pharm., 1864, xxxvi, 193; Arch. der Pharm., 1872, cc, 256.

⁴ Wiggers, Ann. der Pharm., 1832, i, 129; Bonjean, Hist. de seigle ergoté, Paris, 1842; Traité théorique et pratique de l'ergot de seigle, Paris, 1845.

⁵ Kobert, Arch. f. exper. Path. und Pharm., 1884, xviii, 316; Keller, Schweiz. Wehnschr. f. Chem. und Pharm., 1896, xxxiv, 65.

⁶ Jacobi, Arch. f. exper. Path. und Pharm., 1897, xxxix, 85.

Thanks to the work of Barger¹ and his associates, we now believe that ergot contains at least two alkaloids, *ergotinin* and *ergotoxin* (present to extent of 0.2 to 0.3 per cent.), together with a series of active amines, especially *para-hydroxy-phenyl-ethyl-amin* (tyramine), *phenyl-ethyl-amin*, *iso-amylamin*, and β -*imin-azolyl-ethyl-amin* (histamine). Tanret² has added a third base, *ergothionein*, which Barger and Ewins³ show is β -2-thiolglyoxalin-4 (or 5)—propionibetaine, a base closely related to histidine. A further amine has also been found by Engeland and Kutscher,⁴ called *agmatin*, a guanidyl-butyl-amine related to arginine. Trimethyl-amine is found as a decomposition product of choline in the ergot. As these amines are, in reality, putrefactive bases,⁵ it is probable that their presence in varying amounts is due to gradual decomposition of ergot, the therapeutic activity of ergot possibly being closely related to these amine bodies, as ergotinin is inert and ergotoxin is present in such small amounts that the entire ergot action can hardly be attributable to this latter alkaloid alone.⁶ Besides the above we find acetylcholine and a number of physiologically inert substances, so far found only in ergot, such as secale aminosulphonic acid; secalonic acid, a crystalline coloring-matter; sclererythrin, the characteristic red coloring-matter; clavicepsin, a glucoside; ergosterol and fungisterol. Further, ergot contains a large number of substances of general physiologic importance, also found elsewhere, such as fat; various amino acids, as leucine, isoleucine, valine, and aspartic acid; several amines other than those mentioned above, such as putrescine, cadaverine, betaine, uracil, and vernine.

Ergotinin ($C_{35}H_{39}N_5O_5$) was first isolated in pure condition by Tanret,⁷ although its properties and chemical formula were elaborated by Kraft⁸ and, independently, by Barger and Carr.⁹ It is the anhydride of ergotoxin, the two alkaloids being interconvertible. It crystallizes from alcohol in long needles, the sides of which are not quite parallel; the ends are symmetrically replaced by a pair of faces and the extinction is straight. If heated rapidly, it melts at 230° to 231° C. (446° to 447.8° F.). At 18° C. (64.4° F.) it dissolves in 292 parts of ethyl alcohol, in 1020 parts of absolute ether, in 91 parts of ethyl acetate, and in 26 parts of acetone; in 77 parts of boiling benzene, in 52

¹ Barger, Carr, and Dale, Brit. Med. Jour., 1906, ii, 1792; Barger and Carr, Chem. News, 1906, xciv, 89; Jour. Chem. Soc., 1907, xci, 337; Barger and Dale, Biochem. Jour., 1907, ii, 240; Proc. Physiol. Soc., 1909, p. 77; Barger, Jour. Chem. Soc., 1909, xcv, 1123; Barger and Ewins, Ibid., 1910, xcvii, 284; Walpole, Ibid., 1941; Barger and Dale, Ibid., 2592; Ewins, Biochem. Jour., 1914, viii, 44; Barger and Ewins, Jour. Chem. Soc., 1918, cxiii, 235; Barger, Pharmaceutical Jour., 1920, cv, 470; see Spiro and Stoll, Schweiz. med. Wehnschr., 1921, li, 525; Rothlin, Schweiz. med. Wehnschr., 1922, 52, 978.

² Compt. Rend. Acad. des Sci., 1909, cxlix, 222; Jour. Pharm. Chem., 1909, xxx, 145.

³ Jour. Chem. Soc., 1911, xcix, 2336.

⁴ Zentralbl. f. Physiol., 1910, xxiv, 479.

⁵ See Barger, Allen's Commercial Organic Analysis, 1913, vii, 341.

⁶ See Crawford, Amer. Jour. Pharm., 1911, lxxxiii, 147.

⁷ Compt. Rend. Acad. des Sci., 1875, lxxxi, 896.

⁸ Arch. der Pharm., 1906, ccxlv, 366; 1907, ccxlv, 644.

⁹ Jour. Chem. Soc., 1907, xci, 337.

parts of boiling ethyl alcohol, and in 56 parts of boiling methyl alcohol. Extremely soluble in chloroform and almost insoluble in ether. Its solutions have a bluish-violet fluorescence, especially when acidified. It is strongly dextrorotatory. On boiling the alcoholic solution of ergotinin, transformation to the ethyl-ester of ergotoxin gradually takes place, accompanied by a fall in the rotation of the solution. Hence, recrystallization from alcohol should be carried out rapidly to minimize loss of material. The basic properties of ergotinin are feeble, no crystalline salts being known. Ergotinin is readily converted into ergotoxin by the action of alkalis and acids in aqueous solution; the reverse change is brought about by heating ergotoxin with methyl alcohol or with acetic anhydrid.¹ Ergotinin is inert pharmacologically.

Ergotoxin ($C_{35}H_{41}N_5O_6$) was first isolated by Kraft, who called it hydro-ergotinin, and later studied by Barger and Carr. It is a white amorphous powder, melting at 160° to 164° C. (320° to 327.2° F.). It is more soluble in organic solvents than is ergotinin, especially in cold alcohol, although it is not readily soluble in ether. The salts of ergotoxin crystallize well, the phosphate being more easily purified than any of the salts. Ergotoxin phosphate crystallizes from boiling 90 per cent. alcohol with 1 molecule of water of crystallization, forming slender needles generally arranged in groups radiating from a center; if not pure, the crystals may be spheroid. This salt melts at 186° to 187° C. (366.8° to 368.6° F.), with decomposition, and dissolves in 313 parts of cold and in 14 parts of boiling 90 per cent. alcohol. As ergotoxin contains a carboxyl group, it is readily esterified. Both ergotoxin and ergotinin give precipitates with the usual alkaloidal reagents, even when in very dilute solutions, Mayer's reagent being the most delicate, producing a faint opalescence in dilutions of 1 part per million of these alkaloids.

Ergotoxin produces, on intravenous injection in mammals, a somewhat prolonged rise of blood-pressure and, also, contraction of the uterus. Continued administration of doses too small to be immediately fatal produces gangrene (studied experimentally by the bluing of the cock's comb).² Ergotoxin is, also, probably responsible for the chronic effects known as "ergotism."

Tyramin ($C_8H_{11}NO$), p-hydroxyphenylethylamin, is not toxic, although it is probably responsible for the pressor action of aqueous extracts of ergot. This amin is closely related chemically and pharmacologically to epinephrin and exerts its effects chiefly on the blood-pressure, although it has slight action on the uterus.³

Histamin ($C_5H_9N_3$), β -iminazolyethylamin, sometimes called ergamin, lowers the blood-pressure and very powerfully stimulates the uterus.⁴ Its presence, as such in ergot, has been demonstrated by physiologic means within half an hour of collecting it from the rye, but the amount in liquid extracts is probably increased by such processes

¹ See Barger, Allen's Commercial Organic Analysis, 1913, vii, 17.

² See Barger and Dale, Biochem. Jour., 1907, ii, 240.

³ See Dale and Dixon, Jour. Physiol., 1909, xxxix, 25.

⁴ See Dale and Laidlaw, Jour. Physiol., 1910, xli, 318; 1911, xliii, 182.

as prolonged extraction and dialysis. In this connection the work of Koessler and Hanke¹ is of special moment, as showing the origin and action of the proteinogenous amines.

It will be seen, from the above discussion, that several constituents of ergot exert a uterine action, and it is not known which of these is the most important in the effects of the crude drug. The galenic preparations must vary in composition according to the solvent. The alcoholic fluidextract probably owes its activity mainly to ergotoxin; the aqueous preparations, including the solid extracts and "ergotins," owe theirs probably to the amines, particularly to histamin. The isolated principles have not been used sufficiently to permit of a decision as to whether or not they can take the place of the natural mixture.²

Symptoms of Ergot Poisoning.—**Acute poisoning** by ergot may be caused either by the eating of bread made from diseased grain or by preparations of the drug taken internally.³ The symptoms, which may not appear for some hours, usually begin with vomiting; there are burning pains in the abdomen and tingling of the extremities, great thirst, weakness, and diarrhea. There is frequently swelling of the face and extremities. The pulse is slow and weak. Abnormal sensations develop in the skin, especially in that of the hands and feet; there are feelings of chilliness and, later, twitchings or tonic contractions of the muscles. Ataxia, epileptiform convulsions, and mania have been observed. These symptoms are followed by a fall of temperature, and in many cases gangrene of the skin has been observed. Suppression of the urine, great prostration, coma and death from respiratory and cardiac failure may follow. Death may occur in a few hours or be delayed for a few days. If the patient recovers, abnormal sensations may persist for several days; swallowing may be difficult and painful. Sometimes a cataract forms in one or both eyes. Githens⁴ has recently shown that, in rabbits, doses of 2 mg. of ergotoxin per kilo cause a striking rise in temperature, beginning ten to thirty minutes after the injection and reaching its maximum two hours later. This rise varies from 3° to 4.5° C., and is associated with strong tremors and convulsive jerks of the leg.

If the patient taking the excessive dose of ergot be pregnant, and especially if there is a predisposition to miscarriage, abortion followed by severe hemorrhage may occur, leading to death of both mother and child. These results are especially liable to occur in the late stages of pregnancy. Powerful contractions of the uterus may be set up by ergot if there are fibroids present.

Chronic poisoning by ergot has nearly always been due to the eat-

¹ Jour. Amer. Chem. Soc., 1918, xl, 1716; Jour. Biol. Chem., 1919, xxxix, 497, 521, 539, 585; Ibid., 1920, xlii, 521, 527, 543, 557, 567, and 579; Ibid., 1922, l, 131, 193, 235 and 271.

² See New and Non-official Remedies, 1916, p. 113.

³ See Oldright, Canadian Med. Jour., 1870, vi, 404; Meadows, Med. Times and Gaz., 1879, ii, 397; Davidson, Lancet, 1882, ii, 526; Débierre, Bull. gén. de Thérap., 1884, cvi, 52; Faulkner, New York Med. Jour., 1884, xxxix, 668; Hulme, Medical News, 1887, li, 538.

⁴ Jour. Pharmacol. and exper. Therap., 1917, ix, 360.

ing of bread made from diseased grain.¹ Wide-spread epidemics of "ergotism" occurred in Europe during the Middle Ages, but are now rare. More rarely the medicinal use of ergot has led to chronic poisoning.

There are two distinct forms of ergotism, the spasmodic and the gangrenous types. In some epidemics both forms are present, but, as a rule, one form is much more prevalent than the other. The early symptoms are the same in each, and consist in indefinite pains, disturbance of digestion, etc. In spasmodic ergotism there is anesthesia of the fingers and toes, then of the extremities; later there are tetanic spasms of the muscles, followed, if the patient recovers from the first effects, by contractures of the limbs. Mental weakness or dementia is a not uncommon result. In the gangrenous form of ergotism there is acute pain in one or more limbs; the limb swells, is dark in color, and is very cold. Dry gangrene sets in, and fingers, toes, and even arms and legs and nose fall off; there is little pain or hemorrhage. Gangrene of internal organs may occur. Cataracts are common. All these effects seem to be due to ergotoxin, which causes prolonged contraction of the vessels, followed by hyaline thrombosis.

Fatal Dose and Period.—Ergot and the preparations of ergot vary so greatly in strength that it is impossible to state the fatal dose. Thirty grains (1.95 gm.) have caused severe poisoning,² but recovery has followed 150 grains (9.72 gm.). Gangrene and death are said to have followed 12 grains (0.77 gm.). One fluidram (3.75 c.c.) of the fluidextract caused great sleepiness, swelling and redness of the feet, and violent prickling of the extremities³; yet ounce doses have often been given without causing any poisonous symptoms. Death has occurred within one to three days after the appearance of the first symptoms. Death is more likely to follow the long-continued use of small⁴ or medicinal doses than after one large dose. According to Barger,⁵ 0.3 gram of ergotoxin per day must be something like the upper limit of the amount required to produce serious gangrene. There is, however, considerable evidence of idiosyncrasy, and with malnutrition, smaller amounts may have sufficed.

Treatment.—This consists in washing out the stomach and emptying the bowels by enemata or purgatives, such as calomel or castor oil. In collapse, warm baths with cold affusions are recommended; also stimulants, such as strychnin, coffee, tea, etc. If gangrene sets in, the parts should be bathed with warm water and wrapped in cotton.

Postmortem Appearances.—There is rapid putrefaction of the tissues. Hyperemia and ecchymotic areas may appear in the stomach and intestines, these tissues not infrequently showing evidence of very intense inflammatory processes. The kidneys, uterus, and lungs may

¹ See Kobert, *Arch. f. exper. Path. und Pharmakol.*, 1884, xviii, 346; Moricz, *Orvosi hetilap.*, 1908, lii, 543; Kolosoff, *Russk. Vrach.*, 1911, x, 1803 and 1842.

² See Meadows, *Med. Times and Gaz.*, 1879, ii, 397.

³ See Faulkner, *New York Med. Jour.*, 1884, xxxix, 668.

⁴ See Davidson, *Lancet*, 1882, ii, 526.

⁵ *Pharmaceutical Jour.*, 1920, cv, 470.

also show hyperemia. Microscopic examination sometimes reveals evidence of polyneuritis and endarteritis.

Chemical Tests.—On account of the relatively easy transformation of ergotin into ergotoxin, and vice versa, it is at present impossible to differentiate these alkaloids by characteristic chemical reactions. However, certain color reactions may be regarded as characteristic of the alkaloids of ergot, without reference to the specific alkaloid involved.

1. If concentrated sulphuric acid be overlaid with a solution of the alkaloids in ether or ethyl acetate, a transitory orange coloration is produced, which passes through violet to blue. (Tanret's test.)

2. If a small amount of the alkaloids be dissolved in a few drops of concentrated sulphuric acid and a trace of ferric chlorid solution be added, the mixture acquires an orange-red color changing to deep red and, at the margins, appears bluish or greenish blue. (Rosenthaler's test.)

3. To a small amount of the alkaloids dissolved in a few cubic centimeters of glacial acetic acid add a trace of ferric chlorid solution. Cautiously float this solution on concentrated sulphuric acid, when a brilliant violet or an intense blue is produced at the zone of contact. (Keller's test.) In this as in the preceding test hydrogen peroxid may replace the ferric chlorid, as Wolter has shown.¹

Separation from Tissues.—Dragendorff² found it impossible to identify ergot by the isolation of any of its active constituents from animal tissues. This failure was, probably, due to the fact that he worked at a time when little was known concerning the true active principles of ergot. Following the procedure of Dragendorff in examining tissues for alkaloids, Rosenbloom and Schildecker³ were able to isolate from the tissues in a case of acute ergot poisoning a crystalline residue, found in the chloroform extract from acid solutions. This residue was in the form of long needles, showing the morphology and chemical reactions of ergotin.

GELSEMIUM AND ITS ALKALOIDS

The rhizome and root of *Gelsemium sempervirens*, the yellow jessamin or jessamin, a beautiful and fragrant climbing vine of southern United States, are official and actively poisonous. The toxic alkaloid, gelsemin, was first found in the root by Wormley in 1870 as an amorphous product.⁴ In 1882 Gerrard⁵ concluded from his work that the former product of Wormley was not pure and that gelsemin was a crystalline alkaloid forming crystalline salts. Thompson⁶ in 1887 seemed to verify the work of Gerrard and isolated a further alkaloid substance, of amorphous nature, to which he gave the name of gelseminin. This

¹ Chem. Ztg., 1918, xlii, 446.

² Ermittlung von Giften, 1895, p. 294.

³ Jour. Amer. Med. Assoc., 1914, lxiii, 1203.

⁴ Amer. Jour. Pharm., 1870, xlii, 1.

⁵ Pharm. Jour. and Tr., 1882, 3 S., xiii, 502 and 641; Amer. Jour. Pharm., 1883, iv, 256.

⁶ Pharm. Jour. and Tr., 1887, 3 S., xvii, 606 and 805; Pharm. Era, 1887, p. 3.

second alkaloid was found to be much more toxic than gelsemin, Cushny regarding it as a powerful poison resembling coniin. There has been much confusion in medical literature as to the naming of these alkaloids, as the German writers refer to "crystallized gelseminin," which is in reality, Gerrard's gelsemin. Whether the amorphous gelseminin was, in reality, a distinct alkaloid, a polymerized form of gelsemin, a mixture of various uncrystalline principles of unknown composition, or a mixture of actually crystalline products, was not determined until the exhaustive work of Sayre¹ and his colleagues showed conclusively that this supposed alkaloid of Thompson was not a unitary substance, but a mixture of three alkaloids, one of which is crystalline, one capable of forming a crystalline salt, and one distinctly amorphous and possibly colloid, the names of these alkaloids being given by Stevenson and Sayre as sempervirin, gelsemidin, and gelsemoidin respectively.

Further, gelsemium has been shown by various workers, since its discovery by Wormley, to contain a non-nitrogenous compound, highly fluorescent in its solutions, slightly acidulous, and recognizable in small quantities by analysis, which has been named gelsemic acid. All of these substances will be discussed in detail later.



FIG. 51.—*Gelsemium sempervirens*.

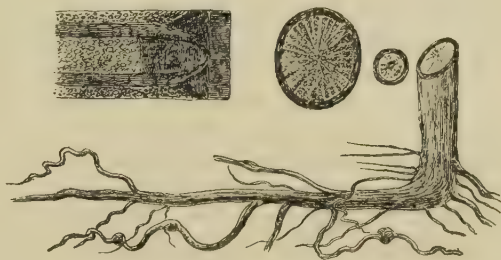


FIG. 52.—Rhizome of *Gelsemium sempervirens*.

Preparations of the green or fresh rhizome are of greater medicinal value. While the presence in the root of a poisonous resin has been denied by some workers, yet this is shown to be an important factor by the following statement of Sayre: "The difficulty involved in the isolation and separation of the constituents of gelsemium has been due largely to the fact that the peculiar intractable resin-like body (a resinoid differing from the ordinary members of this class) permeates the extractive (or alkaloidal) substances, which is difficult to separate from the latter without losing these alkaloidal constituents or masking them in a way that leads one to the conclusion of former investigators that some of these active principles are uncrystallizable."

¹ Proc. Amer. Pharm. Assoc., 1905, liii, 282; Ibid., 1906, liv, 384; Ibid., 1907, lv, 352 and 356; Ibid., 1908, lvi, 851; Ibid., 1909, lvii, 902; Ibid., 1910, lviii, 949; Jour. Amer. Pharm. Assoc., 1912, i, 458; Ibid., 1914, iii, 314; Stevenson and Sayre, Ibid., 1915, iv, 60 and 1458; Sayre and Watson, Ibid., 1919, viii, 708. See also Moore, Jour. Chem. Soc., 1910, xcvii, 2223.

Persons are reported to have been poisoned by eating honey gathered by the bees from gelsemium flowers. "Specific gelsemium," in use by eclectic physicians and others, is prepared from the green root, preserved in transportation to the laboratory by adding 10 gallons of alcohol to the barrel of cut roots (Lloyd). The official preparations of gelsemium are the extract, fluidextract, and tincture. The alkaloids are unofficial.

Symptoms of Gelsemium Poisoning.—The symptoms of gelsemium poisoning resemble those of coniin so closely that distinction is difficult. This toxic action is due, almost entirely, to the group of alkaloids isolated by Sayre and others from the amorphous gelseminin, as gelsemin is more or less inert in the case of mammals. The combined action of the three alkaloids: sempervirin, gelsenidin, and gelsemoidin, differs from that of coniin in that it is more depressant to the central nervous system.

The general symptoms, noted in gelsemium poisoning, may be summed up as follows: Disturbance and relaxation of the muscles of the eye, double vision, dilatation of pupils (either as a general effect or by local application) with loss of power of accommodation; dropping of the lower jaw; great general prostration and muscular relaxation; slow pulse, the action of the heart seeming to depend on the respiration; low temperature; respiration at first quickened and then slow and shallow; mind unaffected, except as a result of failing respiration. Death is due to respiratory failure induced by paralysis of respiratory center.

Fatal Quantity.—It is recorded that 12 minims (0.8 c.c.) of the fluidextract proved fatal to a child three years old; three teaspoonfuls of the fluidextract caused the death of a woman; four doses each of 15 minims of the fluidextract, repeated at short intervals, caused the death of a healthy man in less than four hours after the last dose was taken; and 15 grains (0.97 gm.) of the "resinoid" caused death in an adult. Wormley found that 8 fluidounces (236 c.c.) of the fluidextract yielded 3.2 grains (0.2 gm.) of alkaloid.

Period When Fatal.—Death usually occurs in from one to eight hours. In one recorded case death occurred within one hour. The symptoms begin almost immediately after absorption into the circulation.

Treatment of Gelsemium Poisoning.—The stomach is to be evacuated and repeatedly washed out with warm water. The warmth of the body and the circulation of the blood are to be promoted by internal and external stimulation, such as hot drinks, friction, external heat. The respiration should be stimulated in every way, including the efforts of the patient in the earlier period and artificial movements later on, to carry the patient over the brief duration of gelsemium poisoning. Digitalis has been recommended in hypodermic administration to strengthen the heart, also the joint use of morphin and atropin to strengthen the respiration, but there is not enough known of the effect of any of the narcotics to warrant their use further than to give relief under close observation.

Cases of Poisoning by Gelsemium.—Wormley,¹ in his studies of this drug, states "of 25 cases of gelsemium poisoning that we have collected (some private), 13 proved fatal. Witthaus² says, "Of 40 cases which have been reported there are but 5 in which the responsibility for administration has been questioned." In other words, practically all of the cases of gelsemium poisoning are accidental.

CASE 1.—Man took by mistake a tablespoonful of Tilden's fluidextract of gelsemium. Soon face became congested, pupils dilated but were still sensitive to light, lids were partially closed and there was inability to move them, tongue was thick, skin warm and moist, pulse small and feeble, respirations slow and irregular, no vomiting or purging. Later the respiration became spasmodic, the skin cold, and the pulse imperceptible, death resulting two and a half hours after taking the drug.³

CASE 2.—Boy, eighteen months old, took 30 drops of the fluidextract of gelsemium. In about fifteen minutes he showed marked nausea with retching and vomiting. He was difficult to arouse and soon passed into a stupor, which continued until he died three hours after taking the drug.⁴

CASE 3.—Dr. Parsons has given the following description of his symptoms after the accidental taking of a dram of the fluidextract. In a few minutes there was giddiness, nausea, strabismus, paralysis of the muscles of the mouth and throat, and muffled speech. The eyelids dropped and deglutition became impossible. The voluntary muscles were entirely unimpaired, and sensation and consciousness were perfect. Then there was noted precordial oppression and difficulty of respiration, which later increased rapidly, the inspiration being short and rapid, followed by three or four long gasps. Respirations apparently ceased, he became livid, rolled in agony, felt himself becoming stiff, and then lost consciousness. Up to this loss of consciousness the pulse had remained regular and full. He recovered gradually, the paralysis of the mouth, the muffled speech, and the dropping of the eyelids continuing for some hours. After return of consciousness (two and a half hours after taking the drug) the recovery was rapid, the most marked symptom being a persistent and depressing numbness in the occipital region, which lasted for some hours.⁵

Postmortem Appearances.—For the most part these, as so far found, are normal, except superficial venous injection and congestion of some of the organs.

Properties of the Alkaloids.—Thanks to the work of Sayre and his colleagues, our knowledge of the alkaloids of gelsemium has been greatly advanced. As previously stated, there are four alkaloids which have been isolated from this plant, one of which is crystalline, two amorphous, but capable of forming crystalline salts, and a fourth distinctly amorphous and possibly colloid. While it is possibly true that in the systematic procedure for isolation of these alkaloids in toxicologic work, the three alkaloids, which have been isolated from the former alkaloid known as gelseminin, may remain grouped, and thus give the reactions which we have known as those of gelseminin, yet we must bear the fact in mind that we may obtain any and all of these in our work, and hence must be on the lookout for the variation in the chemical tests made with our suspected residues.

Gelsemin.—This is the most abundant and only ether-soluble alkaloid of gelsemium; its ether residue is a reddish, amorphous mass

¹ Amer. Jour. Pharm., 1882, liv, 337.

² Medical Jurisprudence, Forensic Medicine, and Toxicology, 1911, iv, 937.

³ Davis, Amer. Jour. Med. Sci., 1867, liii, 271.

⁴ Harris, Chicago Med. Jour., 1868, xxv, 760.

⁵ Parsons, Lancet, 1878, i, 953.

having a resinous appearance; its hydrochlorid is pure white, crystalline, soluble in water and difficultly soluble in alcohol. The aqueous solutions of its salts are precipitated by the general alkaloidal reagents. Further, it is precipitated from solutions of its salts by free alkalies as well as by carbonates and bicarbonates, these precipitates being soluble in an excess of the reagent. While Sayre states that the alkaloid itself is amorphous, other workers affirm that it crystallizes from benzene or acetone in pale yellow or colorless glistening prisms of a melting-point of 178° C. (352.4° F.) according to Moore, while Goeldner as well as Schmidt give this as 160° C. (320° F.). It is highly probable that the various workers have not been handling the same substance.

Sempervirin.—The free alkaloid crystallizes from chloroform in reddish-brown needles; it is slightly soluble in alcohol and water and almost insoluble in ether, benzene, and petroleum ether; its hydrochlorid is readily soluble in water and alcohol and is precipitated by nitric, tannic, and picric acids; by potassium chromate, platinic chlorid, sodium chlorid, and sodium nitrate forming yellow precipitates. The nitrate is somewhat soluble in water, very soluble in hot water and in hot alcohol. These solutions give precipitates with Wagner's and Mayer's reagents.

Gelsemidin.—This is an amorphous alkaloid, insoluble in ether, soluble in chloroform and alcohol; its hydrochlorid is insoluble in ether and chloroform, soluble in alcohol, and extremely soluble in water; its crystalline form is granular. Like sempervirin, gelsemidin exists in gelsemium in very small quantity.

Gelsemoidin.—This is an amorphous alkaloid, insoluble or nearly so in ether, soluble in alcohol, chloroform, and water; it does not form crystalline salts; its hydrochlorid is soluble in the same solvents as the alkaloid itself and is hygroscopic; it is separated from the ammonia-soluble resinous matter (once thought to be alkaloid) by means of water or acidulated water in which it is soluble; it exists in gelsemium in small quantity.

Chemical Tests for the Alkaloids.—If a colorless or very nearly colorless residue consisting of gelsemium alkaloids, on white porcelain, be touched with concentrated sulphuric acid the residue dissolves with a slight yellowish to brownish color. If now a minute solid fragment of potassium dichromate, manganese dioxid, or cerosoceric oxid be drawn through the solution by means of a fine pointed glass rod, a fine reddish-purple or cherry-red coloration is developed in "reddish-purple streaks along the path of the crystal," the color bearing more upon the bright red tint if cerosoceric oxid be employed. This color passes into a blue green. According to Wormley,¹ 0.0001 grain will respond to this test, and even one-tenth of this quantity may produce the reddish-purple coloration. It is to be said that this reaction might be confused with that given by strychnin under the same conditions, but the play of colors is entirely different, the initial reddish purple of the gelsemium reaction never being shown as an initial color with

¹ Amer. Jour. Pharm., 1882, liv, 342.

strychnin, as Gerrard¹ states, "In a parallel experiment carried on with strychnin, the two alkaloids cannot be mistaken."

While the above reaction is that usually obtained with the mixed residue of gelsemium alkaloids, it is to be said that the purified and separated alkaloids do not give the same colorations, when treated with sulphuric acid and oxidizing agents, such as manganese dioxid, as Sayre and Watson² have shown. Thus, gelsemin gives a crimson, passing into a green and finally yellow; sempervirin shows an initial green, changing into a yellowish green; gelsemidin strikes an initial purple, passing into a bluish green; while gelsemoidin reacts with an initial purple, passing into a pure green.

The reported color reactions with nitric acid appear to have been subject to the effects of impurities in the alkaloidal residue examined. Thus, Gerrard found no reaction by fully purified gelsemin with nitric acid in the cold, while Barger³ states that "nitric acid dissolves the pure alkaloid with little or no color, but on allowing the liquid to evaporate spontaneously on porcelain, a permanent bluish-green color is obtained even when only a very minute trace of gelsemin is present. As usually obtained, gelsemin residues yield with nitric acid yellowish or brownish-green colorations, rapidly changing to deep green."

Gold chlorid gives, with gelsemin, a yellow precipitate, crystalline, soluble when heated, and containing 37.4 per cent. of gold.

Biologic Tests for the Alkaloids.—Gelsemium alkaloids, $\frac{1}{8}$ of a grain (0.008 gm.) administered hypodermically to a cat, caused marked symptoms in fifteen minutes and death in one hour and a half.⁴ One-sixth grain (0.01 gm.) given to a frog produced, after half an hour, great prostration, followed by tetanic convulsions and death in about four hours.⁵

Cushny⁶ found gelseminin to be intensely poisonous to both frogs and rabbits, causing respiratory failure in both, and also that it dilates the pupil. He found gelsemin to cause tetanic convulsions in frogs, with final deadening of sensory nerve-endings, and to have no effect on rabbits.

Sayre states that it takes 10 mg. of gelsemin hydrochlorid to cause tremors and convulsive movements in a guinea-pig of 450 grams weight, while 3 mg. of gelsemidin hydrochlorid will prove fatal to an animal of similar weight in thirty minutes. This latter alkaloid has a pronounced action on the voluntary muscles, produces loss of co-ordination and a paralytic action on the respiration. One and five-tenth mg. of gelsemoidin hydrochlorid proved fatal to a guinea-pig weighing 425 grams in one and a half hours, the most pronounced action being upon the voluntary muscles and the respiration. With this alkaloid there were several muscular spasms (not tetanic like strychnin) within thirty minutes.

¹ Amer. Jour. Pharm., 1883, lv, 256.

² Jour. Amer. Pharm. Assoc., 1919, viii, 708.

³ Allen's Commercial Organic Analysis, 1913, vii, 30.

⁴ Wormley, Amer. Jour. Pharm., 1882, liv, 338.

⁵ Ibid.

⁶ Ber. d. d. chem. Gesellsch., 1893, xxvi, 1725.

The minimum lethal dose of sempervirin for a frog is 0.00014 gram per gram of frog. The physiologic action of these various alkaloids upon frogs, as reported by Sayre and Watson, is the following: Gelsemin hydrochlorid causes a slow, irregular respiration (30 per twenty-two to thirty seconds), the animal is restless and shows convulsions and slight paralysis; sempervirin nitrate causes the same action on the respiration and the same general behavior of the animal, but there is no paralysis; gelsemidin hydrochlorid produces a nearly normal, regular respiration (30 per sixteen to nineteen seconds), while the animal is quiet and shows a decided paralysis; gelsemoidin hydrochlorid brings about a normal state of respiration, while the animal is quiet and shows some paralysis.¹

Properties of Gelsemic Acid.—This substance was first obtained by Wormley² from the acidulated fluidextract of the root from which extraneous matter had been precipitated by water, washing the concentrated fluidextract with ether, and allowing the ether to evaporate spontaneously. Robbins,³ Sonnenschein⁴ and Schwarz⁵ obtained it by somewhat different methods. It was believed by these latter workers that gelsemic acid was identical with esculin, a glucosid obtained from the bark of horse-chestnut, but Schmidt⁶ has shown that it is identical with scopoletin, a substance isolated from *Scopolia japonica*, and is, chemically speaking, beta-methyl-esculetin with the formula $C_{10}H_8O_4$.

Gelsemic acid, according to Wormley, is a colorless, odorless, nearly tasteless solid, which readily crystallizes, either in groups of prisms or tufts and single needles, or minute plates and scales. It has only a feeble acid reaction and forms definite salts with but few of the metals. It is sparingly soluble in water (1 part in 2912 of water), this solubility being greatly increased by the presence of coloring-matters, and also of the associated alkaloids. It is readily soluble in both ether and chloroform. The melting-point of the crystals is stated to be 160° C. (320° F.) by Robbins, 206° C. (402.8° F.) by Coblentz,⁷ and 197.5° C. (387.5° F.) by Sayre.⁸ Wormley states that "when gradually heated to about 163° C. (325.4° F.) it fuses to a clear liquid, which may be vaporized without change of color or composition."

Chemical Tests for Gelsemic Acid.—1. If a small portion of gelsemic acid be treated with a drop of nitric acid it dissolves with a yellow color to a yellow or reddish solution, the final color depending upon the relative quantity of the organic acid present. On treating this solution with excess of ammonia, it acquires a permanent deep or blood-red color. These results may be obtained from $\frac{1}{10000}$ grain (0.0648 mg.); and even $\frac{1}{50000}$ grain will yield a marked reddish coloration (Wormley). This reaction is shown, also by esculin, so that it is not distinctive.

¹ Jour. Amer. Pharm. Assoc., 1919, viii, 708.

² Amer. Jour. Pharm., 1870, xlii, 1; Ibid., 1882, liv, 337.

³ Dissert., Berlin, 1876.

⁴ Ber. d. d. Chem. Gesellsch., 1876, ix, 1182.

⁵ Dissert., Dorpat., 1882; Pharm. Jour. and Trans., 1882, 3 S., xiii, 148.

⁶ Arch. d. Pharm., 1898, cexxxvi, 236.

⁷ Proc. Amer. Pharm. Assoc., 1897, xlv, 224.

⁸ Ibid., 1907, lv, 352.

2. Sulphuric acid slowly dissolves pure gelsemic acid under a yellow color to a yellow solution, which is unchanged by a moderate heat. If the organic acid is impure, the cold sulphuric acid solution may have a reddish color, changed to deep brown by a moderate heat. If a drop of aqueous ammonia be allowed to flow into a drop of a sulphuric acid solution of gelsemic acid, the latter immediately separates as a mass of crystalline needles. One thousandth grain of the acid will yield a very copious crystalline deposit. This is one of the most delicate and characteristic reactions of gelsemic acid. Esculin fails to respond to this test.

3. Ammonia and the fixed caustic alkalis cause gelsemic acid to assume an intense yellow color, and quickly dissolve it to solutions having very striking fluorescent properties. When the diluted solution is examined by transmitted light, it has a yellow color; under reflected light, a deep greenish-blue appearance; and under condensed sunlight, an intense blue color along the path of the condensed rays. This fluorescence still manifests itself in solutions containing only $\frac{1}{100,000}$ of the acid, but is quickly destroyed by free acids. This latter property serves to differentiate this acid from quinin and its salts, which reveal their fluorescence in the presence of free acid, but lose it in alkaline solutions.

Biologic Test for Gelsemic Acid.—When $\frac{1}{8}$ grain (0.01 gm.) of this body was administered hypodermically to a frog, in a few minutes the eyes were fluorescent and the animal sluggish. An injection of $\frac{1}{2}$ grain (0.03 gm.) into the peritoneum of the frog was fatal, the animal becoming apparently lifeless in five minutes and the heart ceasing to beat after forty minutes.

Taken together, the available evidences of death by gelsemium poisoning, when fully obtained, are very conclusive.¹

Separation from Tissues and Organs.—The process given under Atropin may be followed, using either ether or chloroform, and saving the ethereal extract from acidulous solution to be examined for the fluorescent body.

Wormley was able to recover from the body and identify both the alkaloid and the fluorescent substance four and a half months after death. In this case three teaspoonfuls of the fluidextract had been taken.

MORPHIN AND OPIUM

General Description.—Opium is “the air-dried, milky exudation obtained from incising the unripe capsules of *Papaver somniferum*, Linné, and its variety *album*, De Candolle (Fam. *Papaveraceæ*), and yielding, in its normal moist condition, not less than 9.5 per cent. of anhydrous morphin.” It is a highly complex body, over 20 alkaloids having been isolated therefrom with others probably undiscovered. These alkaloids exist in combination, especially with sulphuric and meconic acids, while a few are united with acetic and lactic acids.

¹ E. Schwartz, Pharm. Jour. Trans., 1882, Ser. 3, xiii, 148–152.

"With one or two exceptions, the alkaloids of opium are strictly peculiar to *Papaver somniferum*; while, on the other hand, the poisonous alkaloid sanguinarin, which is present in all other papaveraceous plants, does not appear to exist in *Papaver*."

Opium, itself, is obtained "in more or less rounded, mostly somewhat flattened masses of variable size, but usually about 8 to 15 cm. in diameter; externally grayish brown, covered with fragments of poppy leaves and at times with some fruits of a species of *rumex* adhering from the packing; more or less plastic when fresh, becoming hard and brittle on keeping; internally dark brown, interspersed with lighter areas, somewhat lustrous; odor characteristic, narcotic; taste bitter, characteristic." Powdered opium is opium dried at a temperature not exceeding 70°C. (158° F.), reduced to a very fine powder, and yielding not less than 10 per cent. nor more than 10.5 per cent. of anhydrous morphin. This powdered opium "is light brown; consisting chiefly of yellowish brown to brownish red, more or less irregular and granular fragments, varying from 0.015 to 0.15 mm. in diameter; a few fragments of strongly lignified, thick-walled, four- to five-sided or narrowly elongated, epidermal cells of the poppy capsule; and very few fragments of tissues of poppy leaves, poppy capsules, and *rumex* fruits." (For defining descriptions of extract of opium, deodorized opium, tincture of opium, and other official preparations of opium, see the U. S. Pharmacopœia, 9th revision.) These preparations are properly made from powdered opium, and are governed by its limits of morphin strength. This strength may be determined in any preparation by an application or modification of the pharmacopeial methods of assay.¹ In a case of poisoning, a portion of the article used should, if possible, be secured for an analysis for morphin and its quantity, and for meconic acid if the presence of opium be in question.

The alkaloids of opium may be classified in 2 groups²; the morphin group, comprising morphin, codein, pseudomorphin, and thebain; the papaverin group, consisting of practically all the remaining alkaloids. The first group consists of strong bases, which are directly of toxicologic interest; while the members of the second group are comparatively inert. These opium alkaloids form a series, of which morphin is one, and thebain the other extremity, as regards their pharmacologic action. "In morphin the narcotic action is the most striking feature, but as the successive members are taken up, this effect becomes less marked than the reflex stimulation, until in thebain practically no depression can be made out, and the symptoms resemble those of strychnin exactly. In man morphin is much the most dangerous of the opium alkaloids, because death is produced in the narcotic stage through asphyxia. In most animals, however, thebain, codein, and laudanin are more toxic, because the failure of respiration does not occur in the stage of depression but during the convulsions" (Cushny).

The free alkaloids of opium are generally but slightly soluble in water,

¹ See Carlos, *Repert. Pharm.*, 1917, 3 S., xxviii, 1.

² See Macht, *Jour. Pharmacol. and Exp. Therap.*, 1915, vii, 339.

but dissolve more readily in alcohol. In many instances the solutions of the free alkaloids are strongly alkaline to litmus. On the other hand, certain of them (*e. g.*, morphin, narcein, laudanin) exhibit a distinct phenoloid character and form definite compounds with the alkalis. The different behavior of the opium bases to solvents affords a valuable means of distinguishing and separating them. They are precipitated from concentrated solutions of their salts by alkali hydroxids and alkali carbonates, some of the precipitates dissolving in excess of the reagent. Most of the opium alkaloids (except papaverin and laudanosin) have a levorotatory action on polarized light, but the specific rotatory power varies so greatly with the solvent and the concentration of the solution that the fact has a very limited practical value. Many of the opium alkaloids furnish characteristic color reactions when treated with strong acids and oxidizing agents, which, with observation of their melting-point, crystalline form, and behavior with solvents, will suffice for the recognition of most of them when in an unmixed state. Morphin, codein, and thebain may be titrated with ease and accuracy by a standard mineral acid, using litmus or methyl-orange as indicators. On the contrary, the above alkaloids have little or no action on phenolphthalein. Papaverin, narcotin, and narcein do not affect litmus, and their salts may be titrated with standard alkali and litmus, just as if the acids were uncombined, the first two of these showing their feeble basic characteristics by the fact that they are extracted by chloroform from acid solutions. Their salts, especially with such organic acids as acetic and benzoic, are very unstable, many of them being decomposed slowly by cold and rapidly by hot water. Hence, when a compound of the alkaloid with a mineral acid is treated with a neutral solution of sodium acetate, or even with a slightly acid solution, the free alkaloid is precipitated. This reaction not only distinguishes papaverin, narcotin, and narcein from morphin, codein, and thebain, but also from caffen, cocain, coniin, atropin, pilocarpin, strychnin, brucin, quinin, cinchonin, and cinchonidin.¹ The cinchona bases are precipitated if the sodium acetate is at all alkaline.²

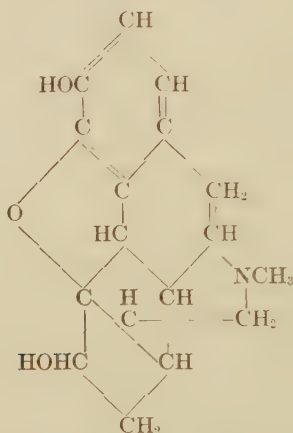
Properties of Morphin and Its Salts.—Morphin is the most abundant of the alkaloids of opium, and the constituent to which the poisonous effects of opium are almost wholly due. The pharmacopeial standard for opium requires not less than 9.5 per cent. of anhydrous morphin.³ As a free base, crystallized morphin has the chemical composition $C_{17}H_{19}NO_3 \cdot H_2O$. It is a monacid, tertiary base, whose nitrogen is in union with 3 atoms of carbon. The 3 oxygen atoms have different characteristics, one being a phenolic hydroxyl, one alcoholic, and the third indifferent, forming a so-called bridge-oxygen atom. Of the 17 carbon atoms of morphin, 14 belong in the phenanthren nucleus, which forms the base of the morphin molecule. While the structure of morphin is still not absolutely settled, yet the work

¹ See Taylor, *Allen's Commercial Organic Analysis*, 1912, vi, 370.

² See Plugge, *Arch. der Pharm.*, 1887, xxiv, 994; *Analyst*, 1887, xii, 197.

³ See Annett, *Biochem. Jour.*, 1920, xiv, 618.

of Knorr, Pschorr, Vongerichten, and others on its probable structure and the associated work of Freund and of Freund and Speyer on the constitution of codein and thebain has almost solved the problem. Based on this work, the most probable graphic structure for morphin is the following¹:



Morphin occurs in colorless or white, shining, rhombic prisms, in fine needles, or as a crystalline powder; odorless; permanent in the air. One gram of morphin dissolves in 3340 mils. of water, 210 mils. of alcohol, 1220 mils. of chloroform, 6250 mils. of ether, and in 100 mils. of lime-water at 25° C. (77° F.); also in 1075 mils. of boiling water and 98 mils. of boiling alcohol; insoluble in benzene. It dissolves in 125 mils. of amyl alcohol at ordinary temperature and in 50 mils. of hot amyl alcohol. The saturated aqueous solution of morphin is alkaline to litmus. Prescott² has called attention to the great influence which the physical condition of morphin has upon its relation to solvents, ether, chloroform, and benzene, dissolving morphin as an amorphous powder or in the freshly precipitated (nascent) condition much more readily than when it exists as a crystalline precipitate; while practically no difference is noted with the action of amyl alcohol. Solutions of sodium and potassium hydroxids, added drop by drop to a morphin solution, precipitate morphin in the crystallized state, but this precipitate is readily soluble in excess of these reagents. The same may be said of barium and calcium hydroxids and, to a limited extent, of ammonia. Heated to about 200° C. (392° F.) morphin turns brown, and melts with partial decomposition at a point variously stated to be 230° C. (446° F.), 247° C. (476.6° F.), and 254° C. (489.2° F.).

Morphin Hydrochlorid (C₁₇H₁₉NO₃ HCl + 3H₂O).—This occurs in white, silky, glistening needles or cubical masses, or as a white crystalline powder; odorless; permanent in the air. One gram of the hydrochlorid

¹ See Pschorr, Ber. d. d. chem. Gesellsch., 1907, xl, 1984; Knorr and Hörlein, Ibid., 3341; Freund, Ber. pharm. Gesellsch., 1919, xxix, 110; see also von Braun, Ber. d. d. chem. Gesellsch., 1919, liiB, 1999; Faltis, Jour. Chem. Soc., 1917, cxii, 411.

² Jour. Amer. Chem. Soc., 1907, xxix, 405.

dissolves in 17.5 mls. of water and 52 mls. of alcohol at 25° C. (77° F.); also in 0.5 mil. of boiling water and 46 mls. of alcohol at 60° C. (140° F.); soluble in glycerin; insoluble in chloroform or ether. Its aqueous solution is neutral or slightly acid to litmus.

Morphin Sulphate ($C_{17}H_{19}NO_3)_2H_2SO_4 + 5H_2O$).—This occurs in white, feathery, acicular, silky crystals, or in cubical masses; odorless; permanent in the air. One gram of the sulphate dissolves in 15.5 mls. of water and 565 mls. of alcohol at 25° C. (77° F.); also in 0.7 mil. of



FIG. 53.—Poppy (*Papaver somniferum*).

water at 80° C. (176° F.) and 240 mls. of alcohol at 60° C. (140° F.); insoluble in ether and chloroform. Its aqueous solution is neutral or slightly acid to litmus.

Symptoms of Poisoning by Morphin or Opium.—In cases of acute poisoning by opium or by morphin alone taken by the mouth the effects begin to appear, in a probable majority of cases, in from twenty to forty minutes. Taken hypodermically the symptoms appear earlier, and narcotism sooner follows the initial symptoms, the same being measurably true under conditions of very rapid absorption from

the stomach. Quantities much larger than just enough to be fatal usually cause a preponderance of comatose symptoms, sometimes from the first. On the other hand, a poisonous quantity not more than enough to be fatal gives rise to the more pronounced and prolonged initial stage—that of mental exaltation and increased action of the heart. Still wider deviations of symptoms and the time of their accession result from the individuality of the nervous system (Cases 16 to 19). Persons differ from one another in the response of the nervous centers to this poison as they differ in reaction against other attacks.

The train of symptoms is made up as follows: A sense of mental exhilaration and physical ease, with both a quickening and a strengthening of the pulse—the initial stage, especially variable, as just stated. Then follow dizziness and heaviness of head, nausea, languor, and drowsiness, the pulse being reduced in frequency some time before it is reduced in force. Nausea comes early in some cases, and if there is vomiting as an effect of the poison, the earlier it occurs the more thorough it is likely to be. In some cases there are itching of the skin and even a sudden eruption. The desire to sleep increases and returns irresistibly in spite of efforts to keep awake. With approaching stupefaction there is gradual loss of muscular power and a diminished sense of feeling. Meantime the pupils of the eyes have become contracted—a distinctive symptom. The sensitiveness of the conjunctiva is diminished, and the pupils fail to respond to light. The respirations have become less and less frequent, and are finally reduced in some cases to three or four a minute, with stertorous breathing. Shallow respiration is often observed. A peculiar respiratory pause or interval is found in some cases, lasting one-half a minute or even longer, followed by somewhat rapid breathing, becoming then gradually slower until, after twenty or thirty respirations, there is another pause (Cheyne-Stokes respiration). Cases have been found in which the pupil would contract at the time of the pause and dilate during the rapid breathing, and the stupor has been found to vary with the same alternation. In other cases the respiration is calm, being gradually reduced from first to last. The breathing gives an index of the action of the poison upon the respiratory nerve-center, the one point where death is threatened and defense is made. With slow or interrupted respiration the face grows bluish, the lips become livid, the extremities cold, and the body temperature reduced. There are two poisons in the blood—first, the morphin, and then with it, the carbon dioxid of suffocation. The surface is usually moist and clammy. There is often retention of urine. The stupor becomes deeper. The pulse, which has been full but growing slower, finally becomes weak. Generally at the last the pupils dilate. Gauss¹ has shown that therapeutic or slightly toxic doses of morphin do not have a marked effect when administered subcutaneously upon the P_H or the alkali reserve of the blood-plasma of man. According to Sollier² during the intoxication there is an increase in both the red

¹ Jour. Pharmacol., 1921, 16, 475.

² Bull. acad. méd., 1922, 87, 428.

and white blood-cells, a change in the differential count, and a very considerable increase in the viscosity of the blood.

There are wide diversities of symptoms. Sometimes convulsions occur in the later stages, more often with children, and in some cases the convulsions have been of a tetanoid character.¹ Sometimes diarrhea occurs with the vomiting. Vomiting is said to be more liable to occur with opium than with morphin, but it is not uncommon with the latter, and as nature's own treatment, it has saved many lives. As a rule, the secretions other than that of the skin are checked. The period when the cerebral symptoms commence, as well as their character, varies greatly in different individuals. There is generally confusion of intellect rather than delusions, and marked delirium is not common. There has been much disagreement as to the uniformity of the contraction of the pupils. Undoubtedly this disagreement has arisen mainly from neglect as to what period of the attack it was when the pupils were observed. It is only in the last stage that the pupils are generally dilated. Certainly there are cases in which there is no contraction of the pupils, but they may fairly be considered quite exceptional. In the early stages, while the pulse is full, the surface is generally warm and often dry, and the dryness of the skin continues throughout in some cases, but in other cases profuse perspiration attends the later stages, and generally the surface is clammy when the pulse begins to fail in strength. When a poisonous quantity is given in successive portions, the second following during the effects of the first and so on, the symptoms of the first stage are extended, and the results, especially upon the respiration, depend upon the rate of elimination of the poison, in proportion to the individual susceptibility and the quantities taken.

A peculiar relapse has marked some cases, in which, after the symptoms have abated and the person has conversed readily for a time, he then falls rapidly into coma and dies.

In differential diagnosis of morphin poisoning it is observed that, as a rule, it differs from alcohol narcosis in the contraction of the pupil; from cerebral hemorrhage, in the two pupils being alike in contraction; from carbolic poisoning, in showing no white stain in the mouth; and from the narcosis of chloroform or ether, in absence of the odor of these agents on the breath. In whatever diseases and from whatever poisons there are failure of respiration and excessive venosity of the blood, there are certain grave symptoms which are likewise found in morphin poisoning. Then the history of the case must be in part relied upon for a differential diagnosis, and, if possible, the question must be settled by a chemical analysis of the liquid vomited or drawn from the stomach.

Chronic Poisoning by Morphin or Opium.—It is scarcely within the scope of this work to discuss the "opium habit." Besides ordinary cases of adults who take the drug by the mouth or hypodermically there are the more obscure cases of infants habitually dosed with

¹ On many of the lower animals morphin affects mainly the spinal cord (further see Kobert, *Intoxikationen*, 1906, ii, 972). Dr. Taylor states that he has found no record of any cases of persons having full tetanic symptoms from morphin poisoning (On Poisons, 3d Amer. ed., 1875, p. 547).

nostrums containing morphin,¹ and of persons suffering chronic poisoning due to the continued application of an opiate dressing to a diseased surface. The subjects of the opium habit, though very well known to be able to bear without injury large quantities of the poison—ten or more times as much as an ordinary fatal dose—yet sometimes fall as the victims of acute poisoning by the same drug.² The opium eater may exceed his own limit so far as to forfeit his acquired toleration, or this toleration may give way under unusual conditions of the system.

Period When Fatal.—The duration of fatal acute poisoning by morphin or opium, in a considerable proportion of the cases, is from six to twelve hours. It is stated by Woodman and Tidy that death has taken place as early as forty-five minutes and has been delayed as late as four days after the poison was taken. "Of 41 fatal cases, 31 died in times varying from five to eighteen hours, about one-half in from six to ten hours, the most usual time being about nine or ten hours after the poison had been taken. If a patient survives forty-eight hours, the prognosis is favorable."³ The period when fatal depends little, if at all, upon the quantity of poison taken.

Fatal Quantity.—It may safely be said that 2 grains (0.13 gm.) of morphin sulphate is so poisonous a quantity when swallowed as undoubtedly to endanger the life of a person not accustomed to the drug. Haines says: "The average minimum fatal dose of opium for the adult may be placed at about 4 or 5 grains, and that of morphin at about 1 grain."⁴ However large a proportion of persons would recover without treatment from the effects of a quantity no larger than this, it could not be expected that every person would so recover.

Children are relatively more susceptible to morphin poisoning than to the action of most other poisons. The difference in the resisting power of adult persons lies especially in the unequal effect of the poison upon the respiratory nerve-centers, and therefore upon the function of respiration, which is the chief natural means of recovery. (For record of some of the smallest quantities known as yet to prove fatal see Cases 1 to 12.) E. R. von Hofmann states the fatal quantity for average adults to be from 3 to 6 grains (0.2 to 0.4 gm.) of morphin.⁵

¹ The sale of medicines offered to the public at large containing such poisons as morphin without any statement or acknowledgment of the presence of the poison by name is punishable by law under the Food and Drugs Act. The Harrison Narcotic Law, now in effect, requires a strict accounting of all narcotics on hand and, further, permits of the prescribing of opium and its derivatives only by registered physicians and for individuals named in the prescription.

² Compare p. 23 in section on General Principles of Toxicology; see also Giofredi, Arch. ital. de Biol., 1897, xxviii, 402; Ibid., 1899, xxxi, 398; Cloetta, Arch. f. exper. Path. und Pharmacol., 1903, I, 453; Rübsamen, Ibid., 1908, lix, 227; von Egmont, Ibid., 1911, lvi, 197; Biberfeld, Biochem. Ztschr., 1916, lxxvii, 283; Pellini and Greenfield, Arch. Int. Med., 1920, xxvi, 279; Kogerer (Wien. klin. Wehnschr., 1920, xxxiii, 1045) calls attention to the hyposusceptibility of the skin of morphin addicts to the intracutaneous injection of morphin solutions.

³ Forensic Medicine and Toxicology, 1877, p. 335.

⁴ Hamilton's System of Legal Medicine, 1894, i, 441.

⁵ Gerichtl. Med., 1895, p. 690. Kobert (Intoxikationen, 1906, ii, 970) remarks that, in the hypodermic way, morphin has from one to three times the strength and rapidity that it exerts when taken by the mouth.

A quantity of morphin just above the limit of a medicinal dose in any case is really on the border of a *poisonous quantity* in that case.¹ Given a barely poisonous quantity—that is, the smallest one “tending to produce death”—it will depend on a great number of factors just how much more would be enough to carry out the *tendency* to its fatal conclusion.² As to what is the maximum medicinal dose, the physician will be governed in part by the nature of the disease with which he is contending in a given case. For persons of the average susceptibility, or that of people at large while in health, the limit of a medicinal dose given by the mouth has been set by the pharmacopeias of several countries.

Cases are well known of an unusual susceptibility to the action of morphin, so that the person having this idiosyncrasy, as it is termed, suffers poisoning effects from doses not above medicinal limits (see Cases 8, 9, 17).

Treatment of Poisoning by Morphin or Opium.—The chief remedial measures are: (1) To remove the poison from the stomach; (2) to arouse the patient to breathe; (3) the permanganate treatment, if we accept recent testimony; (4) atropin administration as physiologic treatment, urged by many physicians and opposed by some; (5) strychnin, caffein, strong coffee or tea, cocain, and measures to improve the circulation.

1. To remove the poison from the stomach is the first requisite. Generally a simple siphon-tube for the stomach is the best instrument, but a stomach-pump may be used, washing out the stomach two or three times with an abundance of warm water. This should be done even if the poison has been taken in the hypodermic way, because of the abundant discharge of morphin into the stomach from the blood (see Case 23). For the same reason it is well to repeat the washing out of the stomach from time to time. It is most desirable, also, to test the discharges and washings of the stomach for morphin from time to time in order to learn when the poison ceases to appear in the stomach. If sufficient vomiting result from the poison, each act should be followed by copious drafts of warm water. Emetics are employed to the same end, and must be depended upon if opium has been taken in a mass such as might fail to pass the tube. Ground mustard, in teaspoonful doses repeated, or sulphate of zinc, in doses of from 20 to 30 grains (1.2 to 1.9 gm.), is the most suitable emetic. For hypodermic use apomorphin in doses of $\frac{1}{10}$ grain (0.006 gm.) has been employed, but caution must be exercised in this connection, as the asthenia may be increased by its use. To lessen the solubility of the morphin or opium remaining in the stomach and intestines (including the morphin discharged into the stomach from the blood), tea, tannic acid, finely powdered charcoal suspended in water, or iodine in aqueous solution of potassium iodid may be admin-

¹ We may, however, conclude that 4 grains (0.26 gm.) of opium and 1 grain (0.06 gm.) of a morphin salt would, in most cases, prove poisonous doses to an adult (Woodman and Tidy).

² See Tomasinelli, Arch. ital. de. biol., 1908, xlix, 349, and Cæsar, Biochem. Ztschr., 1912, xlii, 316.

istered. No effective "precipitation" of the alkaloid can be accomplished in the abundant and complex liquids of the stomach. After the danger is averted a saline laxative or enema should be given.

2. To *arouse the patient to breathe* stimulation of the respiration and of muscular movement is a necessity.¹ Constant urging to effort in breathing at a good rate and application of the magneto-electric current to the spine and chest, or the galvanic brush to the surface, are measures that can be carried on together. Other means are flagellations by cold wet cloths to the head, face, and back of the neck, pinching of the skin, and ammonia to the nostrils. The patient may be kept walking between two assistants. Artificial respiration, about eighteen times a minute, is a resource not to be neglected when breathing fails. Whatever the respiration responds to must be applied with perseverance to the very last, and whatever remedies are employed, the rate of respiration obtained will serve as a measure of their efficacy.²

3. The *treatment by potassium permanganate*³ is advocated as a means of the oxidation of morphin⁴ (see Cases 25 to 34. As to the chemistry of morphin oxidation see p. 527). When given by the mouth the permanagnate is used in doses of about 1 grain (0.06 gm.) more than the quantity of morphin taken, the remedy being dissolved in 30 or 40 parts of water (or 10 grains—0.65 gm.—in a half tumblerful). Moor recommends administration by the mouth, and also hypodermic administration in a saturated aqueous solution, but Wood and Luff⁵ do not advise the hypodermic use. Sharp⁶ concludes that the action of this agent in the blood of animals is physiologic instead of chemical. Moor advises that a very dilute solution—1 grain (0.06 gm.) to a tumblerful of water—be administered by the mouth during recovery, to act upon the morphin which is being discharged into the stomach.

4. *Atropin Administration*.⁷—As a respiratory stimulant, and not wholly a physiologic antidote to morphin. Atropin sulphate should be given, the earlier, the better, in hypodermic doses, beginning with from

¹ In poisoning by this agent if sufficient respiration can be kept up until the poison is disposed of, all will be well. It is by respiration that, without treatment, more or less of the poison is probably converted into inert oxidation products of morphin.

² George L. Peabody, in Foster's Prac. Ther., 1897, ii, 43: The state of the pulse is valueless as a guide. The sole use of the faradic current is to stimulate respiration.

³ William Moor, Med. Record, New York, 1894, xlv, 200, and articles following in same journal; Brit. Med. Jour., 1895, i, 1369; H. C. Wood, Univ. Med. Mag., Philadelphia, 1894, vi, 747-752; A. P. Luff, Brit. Med. Jour., 1896, i, 1193; L. Sharp, Therap. Gaz., 1895, 3 s., xi, 561, 732.

⁴ The inhalation of oxygen has been proposed and used as a remedy in poisoning by morphin, but has not justified expectations. Crequy, Bull. Gén. de Ther., 1880, xcvi, 133; Limousin, Amer. Jour. Med. Sci., 1880, cvi, 297.

⁵ Loc. cit.

⁶ Loc. cit.

⁷ Kobert (Intoxikationen, 1906, ii, 978) has himself used atropin in treatment of opium poisoning for fourteen years, following von Gräfe and others. He uses $\frac{1}{6}$ grain (0.001 gm.) hypodermic injections every thirty minutes until the pulse improves and the pupils enlarge. H. C. Wood (Boston Med. and Surg. Jour., 1893, cxxviii, 637: Lecture before Harvard Medical School) uses atropin as a respiratory stimulant, combining its effect with that of strychnin. C. H. Lewis (Detroit Lancet, 1879, iii, 193: reports of cases) uses atropin beyond the dilatation of the pupil to improve the respiration and the pulse, regardless of a resulting soporific state.

$\frac{1}{80}$ to $\frac{1}{20}$ grain (0.001–0.003 gm.) at discretion, and according to the intensity of the effects of morphin, repeating as necessary to dilate the pupil and then to improve the respiration (see Cases 40 to 57). Tincture of belladonna by the mouth is not so well governed, but may be given, beginning with 30 minims (2 c.c.).

5. *Strychnin; Caffein; Strong Coffee or Tea; Cocain; Measures to Improve the Circulation.*—Strychnin in such doses as $\frac{1}{32}$ grain (0.002 gm.) hypodermically is advised by H. C. Wood as a respiratory stimulant, more especially when atropin is used. Strong coffee is a common remedy, and caffein hypodermically with equal quantity of sodium salicylate to dissolve in twice its weight of water is a more effective form. Cocain hydrochlorid is indicated in many cases, in hypodermic doses, of from $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.016 to 0.032 gm.). The extremities should be warmed, as indicated, using foot-baths, mustard applications, friction, etc.

CASES OF POISONING BY MORPHIN OR OPIUM

CASE 1.—A pill containing 1 grain (0.06 gm.) of the acetate of morphin, taken by a woman, caused narcotic symptoms in half an hour and death in nine hours.¹

CASES 2-6.—Five cases in which 1 grain (0.06 gm.) of hydrochlorid of morphin proved fatal to adults.²

CASE 7.—Three grains (0.19 gm.) of morphin taken by a mulatto of sixteen years caused death in twelve hours.³

CASES 8 and 9.—According to Christison, 7 drops of laudanum always narcotized a certain gentleman. Half a grain of opium (0.03 gm.) caused narcotism in a woman seen by Grisolle.⁴

CASE 10.—A poultice containing much laudanum applied to the pit of the stomach of a young man caused narcotism and death, although treatment was employed.⁵

CASE 11.—Five drops of laudanum injected into the rectum of a child of eighteen months caused death in six hours.⁶

CASE 12.—Opium, $\frac{1}{20}$ grain (0.003 gm.), caused the death of a child sixteen days old.⁷

CASE 13.—Morphin, 12 grains (0.78 gm.), was taken hypodermically by a girl of nineteen. Respiration was very gravely affected, pulse not affected so much; there was blueness of the face, the pupils contracted to a point, and there was no sensitiveness of the conjunctiva for some hours. Recovery.⁸

CASE 14.—Eight ounces (249 gm.) of crude opium were taken by a pregnant woman of thirty-two years. An hour afterward she was able to give a connected account, and copious vomiting was induced by an emetic. Stupor followed, and later violent burning pain in the stomach. Recovery.⁹

CASE 15.—Crude opium, 180 grains (11.66 gm.), taken by a woman. Symptoms: semicomatose state; slow and feeble pulse; cold skin; relaxed limbs; contracted pupils. Treatment: emetics, strong hot coffee. Recovery.¹⁰

CASE 16.—Seventy-five grains (4.86 gm.) sulphate of morphin taken by a youth of nineteen years. Symptoms began one and a half hours after swallowing the poison, with sleepiness and a staggering gait. Free emesis then obtained by emetics. Patient then became unconscious, respiration slow and labored, pulse

¹ Townsend case, *Phar. Jour. Trans.*, 1872, 3 S., iii, 16.

² With details by Taylor in his work *On Poisons*, 549; see *Lancet*, 1872, ii, 24.

³ Prentiss, *Amer. Jour. Med. Sci.*, 1867, lxxix, 562.

⁴ Wharton and Stillé, *Med. Juris.*, 1884, 341.

⁵ Stillé, *Mat. Med.*, i, 671.

⁶ J. B. Jackson, *Amer. Jour. Med. Sci.*, 1854, liv, 384.

⁷ E. Smith, *Amer. Jour. Med. Sci.*, 1854, liv, 381, report of Wm. Morland on Powerful Effects from Small Quantities of Opium.

⁸ Pope, *Lancet*, London, 1894, i, 669.

⁹ d'Outrepoint, *Amer. Med. Recorder*, 1828, xiii, 418.

¹⁰ J. G. S. Carghil, *Brit. Med. Jour.*, 1879, i, 932.

soft and frequent, pupils contracted "to the size of a pin's point." Remedies, belladonna extract, the cold douche, galvanism. Recovery.¹

CASE 17.—*External application* of about a grain (0.065 gm.) of morphin to a blistered surface at the back of the neck. Patient an aged lady. Symptoms appeared after two hours, consisting of convulsive agitations, cold sweats, extreme prostration, and threatened suffocation. Slow recovery under active treatment.²

CASE 18.—Three grains (0.19 gm.) of morphin *injected into the rectum* of a man of forty years. Symptoms, deep coma and contracted pupils. After ten hours the jaws were found so contracted that they could hardly be opened. There were no convulsions. Treatment, instituted after ten hours' delay, consisted of caffen hypodermically and strong coffee by the mouth. Death occurred in sixteen and a quarter hours.³

CASE 19.—Half an ounce (14.8 c.c.) of laudanum taken by a man of sixty-two years. Symptoms delayed twelve hours, then complete coma, with contraction of the pupils. Treatment with stomach-pump, coffee, and galvanism. Recovery.⁴

CASE 20.—Laudanum, 1½ ounces (44 c.c.), taken by a man of seventy-two years. Symptoms delayed nine hours, then vomiting, after which the pupils were dilated. Recovery in forty-eight hours.⁵

CASE 21.—Two and one-half ounces (74 c.c.) of liquor opii sedativus (Battley's) taken. Total insensibility followed in fifteen minutes; death, in one hour and twenty minutes.⁶

CASE 22.—Symptoms of strychnin poisoning, convulsions, partial opisthotonos, no coma, followed ¼-grain (0.016 gm.) doses of acetate of morphin. Great relief afforded by hydrocyanic acid. Recovery. Morphin found in the urine.⁷

CASE 23.—Ten grains (0.65 gm.) of opium taken by a Chinaman with fatal result. Seven and a half hours after the poison was taken the stomach was washed out, when the washings responded to tests for morphin and for meconic acid. The urine, being drawn by a catheter, gave tests for morphin. From ten to thirteen and a half hours after the poison was taken the washings of the stomach at intervals gave tests for morphin, but gave negative results in test for meconic acid. It is the conclusion of the observer that this morphin must have been discharged from the blood into the stomach.⁸

CASE 24.—A woman of forty-nine years had taken about 1 ounce (28 c.c.) of laudanum. Was perfectly comatose, with stertorous breathing, feeble pulse, ghastly countenance, pupils "at a pin's point," and full muscular relaxation. Under treatment with emetics, flagellation, and coffee recovery occurred.⁹

CASES 25-28.—A man aged fifty-seven took an unknown quantity of morphin. Found in collapse, body cold, face almost purple, pupils contracted, reflexes absent. Death occurred in twelve hours.

A man of twenty-two years took three teaspoonfuls of morphin sulphate. The respirations were shallow and not over 2 a minute, the pulse slow and full, the pupils narrowed to a pin's point, the face cyanosed, the forehead cold and wet with perspiration. Treatment with permanganate. Recovery.

A woman of twenty-five years had taken ½ ounce (14.8 c.c.) of laudanum. The respirations were shallow and slow, face cyanosed, pupils contracted. Treatment with permanganate. Recovery.

A mulatto woman of twenty-one years took 2 fluidrams (7.4 c.c.) of laudanum with the same volume of glycerin. Respiration and heart action but slightly affected, face cyanosed, pupils "at a pin's point." Treatment with permanganate. Recovery.¹⁰

CASE 29.—A man had taken 2 ounces (59 c.c.) of laudanum. Was unconscious, the pupils contracted to the size of a pin-point, the respiration scarcely more than a gasp, the pulse very weak. Treatment, potassium permanganate in hypodermic administration. Recovery.¹¹

¹ W. F. Norris, Amer. Jour. Med. Sci., 1862, lxx, 395.

² Amer. Med. Intelligencer, 1838, ii, 13; Wormley's Micro-Chemistry of Poisons, 2d ed., 1885, 479.

³ Anstie, Med. Times and Gaz., 1863, i, 134.

⁴ Sloan, Ibid., 1855, ii, 445.

⁵ Gibb, Amer. Jour. Med. Sci., 1858, lxi, 288.

⁶ Beck's Med. Juris., 1863, ii, 792.

⁷ Shearman, Med. Times and Gaz., 1857, xiv, 235.

⁸ L. P. Hamburger, Johns Hopkins Hosp. Bull., 1894, xlii, 94.

⁹ J. D. T. Beckett, Lancet, London, 1880, ii, 654.

¹⁰ W. L. Pyle, Med. News, Philadelphia, 1894, lxiv, 514.

¹¹ C. E. Johnson, Ibid., Philadelphia, 1894, lxiv, 104.

CASE 30.—A woman had taken morphin. Was in profound stupor, with respirations 3 a minute, pulse rapid and irregular, countenance livid, extremities cold. Permanganate solution was injected into the arm. Recovery.¹

CASE 31.—A woman of middle age had taken a teaspoonful of morphin. Was in a comatose state. The permanganate treatment was given hypodermically. Recovery.²

CASE 32.—A child of seven years, not in good health, had taken 2 fluidrams (7 c.c.) of laudanum. Was found with respirations 8 a minute, pulse 46 and unsteady, face pallid and shrunken, expression agonized, and skin cold and covered with sweat. Under the permanganate treatment hypodermically the patient recovered.³

CASES 33, 34.—The permanganate treatment, followed by recovery.⁴

CASES 35, 36.—Two cases, a man of thirty-seven and one of fifty-six years, the one having taken 12 grains (0.78 gm.), the other 30 grains (1.94 gm.), of morphin, in each case the respiration nearly failing, were treated with forced respiration and hypodermics of permanganate, with recovery as a result.⁵

CASE 37.—A man had taken 16 grains (1.04 gm.) of morphin sulphate. He was comatose, the respirations were shallow but not decreased in number, the pupils were narrowed to a pin-point, the skin was cold and clammy, and the urine was suppressed. The treatment included the permanganate solution by the mouth and strychnin hypodermically. Recovery.⁶

CASE 38.—A youth of eighteen years had taken 20 grains (1.3 gm.) of morphin sulphate. "He was comatose, with respirations 4 a minute, and pupils 'at a pin's point.'" The treatment was by atropin and strychnin hypodermically, and permanganate both by the mouth and hypodermically, and was followed by recovery.⁷

CASE 39.—A boy of seventeen years had taken 6 grains (0.39 gm.) of morphin sulphate. Was cyanosed, with respirations only abdominal and 40 a minute, pulse 160, and temperature 101° F. In treatment atropin and coffee were used without effect. Then *nitroglycerin*, $\frac{1}{60}$ grain (0.0013 gm.), was given hypodermically, repeated in an hour. Recovery.

CASE 40.—A man received 3.7 grains (0.24 gm.) of morphin hypodermically. His respirations were 8 a minute, pulse 40, temperature in the anus 97.2° F. He was unconscious, and a reddish fluid exuded from his mouth. He was treated with *atropin* hypodermically and recovered.⁸

CASE 41.—A man of twenty-eight years had taken 6 ounces (170 gm.) of opium. He was comatose, with pupils contracted to "a pin's point," and pulse slow and full. Treatment: atropin, artificial respiration, and the faradic current. Recovery.⁹

CASE 42.—A woman had taken by mistake a half-teaspoonful of morphin sulphate. Fifty-five minutes later moderate emesis had just been obtained, and soon after the stomach was well washed out. Atropin sulphate was given hypodermically—at first, $\frac{1}{32}$ grain (0.0027 gm.); then at intervals of fifteen minutes $\frac{1}{16}$ grain (0.004 gm.); and later portions of $\frac{1}{8}$ grain (0.0081 gm.). Coffee was administered, coffee fluidextract hypodermically, and frictions and the faradic current were applied. After the fourth injection of atropin the pupils began to dilate, and in one hour covered about one-half of the iris. "They remained at this degree of dilatation and utterly unresponsive to light, with conjunctiva insensible to touch." During the dilatation of the pupils the respirations continued to grow slower and more shallow, the pulse more frequent and feeble, the surface more cold and pale, with increasing stupor. The administration of the atropin salt was continued six hours, and in all $1\frac{1}{16}$ grains (0.0688 gm.) were given subcutaneously. Five hours after the first dose of atropin the respirations were 7 a minute, the pulse 140. At the time of the last administration the respiration and the pulse began to improve, and five hours later the respirations were 14 and the pulse 100 a minute. The period of profound coma was fourteen hours, after which there was recovery without untoward symptoms.¹⁰

¹ J. S. Carpenter, *Ibid.*, Philadelphia, 1894, lxiv, 699.

² T. J. M. Lindsay, *Med. Record*, New York, 1895, xlviii, 858.

³ C. H. Callender, *Ibid.*, New York, 1894, xlv, 345.

⁴ Ebert and Putnum, *Ibid.*, New York, 1895, xlvii, 301-303.

⁵ J. D. Voorheis, *Ibid.*, New York, 1895, xlviii, 768.

⁶ Walker, *Brit. Med. Jour.*, London, 1896, i, 82.

⁷ A. C. McDonald, *Med. Record*, New York, 1895, xlviii, 466.

⁸ Kobert, *Schmidt's Jahrb. d. Med.*, 1880, clxxv, 15.

⁹ H. H. Taylor, *Lancet*, London, 1884, i, 937.

¹⁰ C. H. Lewis, *Detroit Lancet*, 1879, iii, 193.

CASE 43.—A woman took from 15 to 20 grains (0.97 to 1.29 gm.) of morphin. The respirations were at one period as slow as 2 a minute, the pupils being contracted to a pin-point. Under hypodermic-administration of atropin there was recovery.¹

CASE 44.—A man of thirty-two years had taken 51 grains (3.3 gm.) of morphin. The respirations were very irregular, the face cyanotic, the lips purple, the pupils contracted to a point. After the poison had been in the stomach thirteen hours the stomach-pump was used along with other treatment—atropin, caffen, galvanism, and flagellations. Recovery.²

CASE 45.—A woman of forty-three years had taken 3 drams (11 c.c.) of tincture of opium. The respirations were shallow and irregular, the pulse 90, the pupils contracted, and the patient could not be aroused even with the use of the battery, but rallied under hypodermic administration of atropin.³

CASE 46.—A woman of twenty-nine years had taken 2 ounces (56 gm.) of prepared opium. She was comatose, with respirations 4 or 5 a minute. Treatment, atropin hypodermically. Recovery.⁴

CASE 47.—An infant of three months was given a teaspoonful of laudanum. It became semicomatose, there was vomiting, and the pupils were contracted to a point. Two and a half minims (0.15 c.c.) of solution of atropin sulphate were administered with strong coffee. There was recovery.⁵

CASES 48-57.—Ten cases of poisoning by morphin, treatment with atropin, and recovery.⁶

CASE 58.—A woman of twenty-eight years took 16 grains (1.03 gm.) of morphin sulphate and was found in complete narcosis. Under treatment with hypodermic injections of ammonium carbonate and belladonna life was maintained and the patient rallied.⁷

CASE 59.—An infant of one month was given 3 drops of laudanum. Became semicomatose, and at one time respiration ceased. Artificial respiration with nutrient enemata was employed, and the child recovered.⁸

CASE 60.—A child of fifty-four hours was given $\frac{1}{4}$ grain (0.016 gm.) of morphin. It was found cyanotic, with respirations 3 a minute, and barely perceptible pulse. Under treatment with immersions in hot water, hypodermic injections of whisky, and enemata of strong coffee the child recovered.⁹

CASE 61.—A woman took 92 grains (6 gm.) of opium and became comatose. She was treated with injections of $\frac{1}{3}$ grain (0.02 gm.) of strychnin sulphate and $\frac{1}{4}$ grain (0.01 gm.) of atropin sulphate, and recovered.¹⁰

CASE 62.—A man of twenty-one smoked opium—120 pills containing from 3 to 5 grains (0.19 to 0.32 gm.)—daily for two or three days and was poisoned. Respirations 12 or 13 a minute, pulse feeble and rapid, pupils contracted, and face haggard. He was treated with kumiss and brandy, and atropin hypodermically. Partial recovery.¹¹

CASE 63.—A man took an unknown quantity of laudanum. The respiration failed at times, but was renewed by artificial means. Pupils strongly contracted and not responsive. Twelve hours after the poison was taken the patient died from heart failure.¹²

¹ J. H. Smith, *Med. News*, Philadelphia, 1882, xl, 318.

² G. M. Morse, *Boston Med. and Surg. Jour.*, 1887, cxvi, 603.

³ G. H. Cooke, *Lancet*, London, 1890, ii, 1096.

⁴ B. L. Paton, *Ibid.*, London, 1896, i, 548.

⁵ H. R. Bramwell, *Ibid.*, London, 1889, i, 1113.

⁶ Huber, *Ztschr. f. klin. Med.*, 1888, xiv, 444; Schmidt's *Jahrb. d. ges. Med.*, 1888, ccxx, 22; Alexander, *Glasgow Med. Jour.*, 1886, xxv, 21; Schmidt's *Jahrb. d. ges. Med.*, 1886, ccix, 138; Paster, *Münch. med. Wehnschr.*, 1886, xxxiii, 5; Schmidt's *Jahrb. d. ges. Med.*, 1887, ccxiii, 30; Townsend, *Boston Med. and Surg. Jour.*, 1885, cxiii, 297; Wright, *Ibid.*, 1881, cv, 8; Souwers, *Med. and Surg. Reporter*, 1881, xlv, 533; Eliot, *Med. Record*, 1886, xxix, 555; Wallian, *Ibid.*, 1883, xxiii, 487; Stuver, *Med. News*, 1882, xli, 592.

⁷ W. C. Coffee, *Med. and Surg. Reporter*, Philadelphia, 1882, xlvii, 697.

⁸ W. P. Morgan, *Brit. Med. Jour.*, 1888, i, 850.

⁹ W. Judkins, *Med. Record*, New York, 1885, xxviii, 151.

¹⁰ H. C. Wood, *Univ. Med. Mag.*, Philadelphia, 1894, vi, 747; Roether, Schmidt's *Jahrb. d. Med.*, 1894, cexliii, 24.

¹¹ J. Collins, *Med. Record*, New York, 1889, xxxvi, 288.

¹² H. W. Hayes, *Brit. Med. and Surg. Jour.*, ii, 807.

CASE 64.—In a case of death by morphin poisoning the autopsy revealed interstitial emphysema as a result of long-continued artificial respiration.¹

CASE 65.—A child of three years suffering from scarlatina was given about 1 grain (0.065 gm.) of opium, became comatose, and died two hours after the poison was given. The mucous membrane of the stomach was subacutely inflamed. From the contents of the stomach a trace of morphin and meconic acid estimated at $\frac{1}{160}$ grain (0.00065 gm.) were obtained.²

CASE 66.—A Chinaman of twenty-seven years took 62 grains (4 gm.) of extract of opium. Atropin was used in treatment without much effect. The symptoms were those of morphin poisoning. The autopsy showed hyperemia of the brain.³

CASE 67.—The body of a suicide was found two days after death, morphin, strychnin, and copper salt being found in his room. About 8 grains (0.5302 gm.) of morphin were found in the stomach, a small quantity in the intestines, none in the liver or the gall-bladder, and an abundance in the urine, the blood, and the secretions of the mouth and nose, and none in the brain.⁴

Postmortem Appearances.—Morphin poisoning is not distinguished from other modes of death by any peculiar appearances at the autopsy. The blood-vessels of the brain are commonly very full, and frequently with effusion between the brain membranes and into its ventricles. Congestion of the lungs is generally found. The pupils sometimes remain contracted; more often they are of ordinary size or dilated, as, indeed, in some cases they are before death. The blood is usually fluid and dark in color. Upon opening the stomach the attention should be directed toward perceiving any odor—*i. e.*, whether or not it be that of opium. It is only in case of poisoning with poppy preparations that fragments in the stomach are liable to reveal a source of morphin poisoning. No local irritant action on the mucous membrane results from morphin.

Chemical Tests for Morphin.—In the first place the chemist is to keep in mind the distinctive molecular character of this alkaloid. Its well-known avidity for oxidation is not indiscriminate toward oxidizing agents. The first product of its oxidation is oxydimorphin

¹ M. Mendelsohn, Schmidt's Jahrb. d. Med., 1887, ccxv, 144.

² J. Priestley, Brit. Med. Jour., 1893, ii, 1153.

³ C. Paster, Schmidt's Jahrb. d. Med., 1887, ccxiii, 30.

⁴ Dragendorff's Organische Gifte, 1872, 130. For further cases of morphin and opium poisoning see Lehndorff, Mitt. d. Gesellsch. f. inn. Med. Khde. im Wien, 1908, vii, 179; Shoemaker, Penn. Med. Jour., 1909, xiii, 807; Taylor, Canad. pract. and Rev., 1909, xxxiv, 431; Dufour, Marseille méd., 1909, xlv, 453; Hirschberg, Deutsch. med. Wehnschr., 1909, xxxv, 1357; Swindale, Brit. Med. Jour., 1909, ii, 1467; Charpentier, Lancet, 1910, ii, 885; Claybrook, Jour. Amer. Med. Assoc., 1910, lv, 855; Voigt, Therap. Monatsh., 1911, xxv, 601; Besson, Gaz. méd. de Paris, 1911, lxxxii, 329; Strother, Virginia Med. Semi-Month., 1911, xv, 571; Gerlach, Arch. internat. de méd. leg., 1911, ii, 39; Winternitz, Therap. Monatsh., 1912, xxvi, 169; Michailoff, Voenno-med. Jour., 1912, ccxxxiv, 588; Taylor, Guy's Hosp. Rep., 1912, lxvi, 25; Dickson, Brit. Med. Jour., 1912, i, 724; Mühlfelder, Deutsch. med. Wehnschr., 1912, xxxviii, 778; Hunt, Brit. Med. Jour., 1913, i, 1271; Magnus, Vrtljschr. f. gerichtl. Med., 1913, 3 f., xlv, 1; Rubin, Friedrich's Bl. f. gerichtl. Med., 1914, lxvi, 35; Lorentzen, Ztschr. f. Med.-Beamte, 1914, xxvii, 165; Strasser, Lancet-Clinic, 1914, cxii, 66; Gordon, Jour. Amer. Med. Assoc., 1915, lxiv, 1867; von Sury, Cor.-Bl. f. Schweiz. Aerzte, 1915, xlv, 314; Beates, Med. Council, 1916, xxi, 50; Webster, Analyst, 1917, xlii, 226; Gödde, Deutsch. med. Wehnschr., 1917, xliii, 204; Van Os, Nederl. Tijdschr. v. Geneesk., 1918, i, 23; Joachimoglu, Deutsch. med. Wehnschr., 1919, xlv, 1413; Hankin and Chatterji, Analyst, 1920, xlv, 171; Becker, Med. Klin., 1920, xvi, 467; Joerg, New York Med. Jour., 1920, cxii, 44; Schultz, Therapeut. Halbmonatsh., 1920, xxxiv, 571; Erlendsson, Ugesk. f. Laeger, 1922, lxxxiv, 190.

($C_{17}H_{18}NO_3$)₂, or pseudomorphin. By further oxidation it yields a number of distinctive color-products, undetermined members of known series, variable derivatives of the several color roots of morphin. The color-forming roots obtained as the ultimate chemical fragments of the morphin molecule are morpholin,¹ phenanthrene, and possibly derivatives of naphthalene. The synthetic product named by Chastaing "morphin-blue"² gives example of these color compounds. There are also a phenolic hydroxyl and an alcoholic hydroxyl, causing other reactive capabilities of morphin, its free solution with fixed alkalis, its picric-acid-like products with nitric acid, its ready conversion to codein and to other derivatives by substitution of acid or alcohol radicles.

When morphin or one of its salts is taken or obtained by itself—that is, nearly or quite free from intermixed matters—it can be identified by tests as follows:

1. **Tests by Iodic Acid.**—There are two very different iodic-acid tests for morphin; these are—(1) The test with iodic acid followed by ammonia (Lefort's test), giving the mahogany color of a morphin derivative; (2) the ordinary test with iodic acid and starch, giving simply liberated iodine and a blue color. The test with iodic acid and ammonia is distinctive of morphin; the test without ammonia, although it has been much more in use and in the books, is not distinctive of morphin, but is a test for any reducing agent of sufficient intensity. The two tests are equally delicate: the former (Lefort's) has positive value in proof of the presence of morphin; the latter (without ammonia) has negative value in proof of the absence of morphin. In both tests the iodic acid acts as an oxidizing agent upon the morphin. The ammonia used in Lefort's test at once decolors the iodine and develops the color of the morphin-oxidized product. Either of these tests may be made upon a spot of dry residue from evaporation, or upon a just perceptible fragment of a solid to be tested; in either case on the white surface of a clean dry porcelain evaporating dish.

For the test distinctive of morphin (Lefort's) add a drop of a solution of iodic acid and leave for ten minutes. If the color of free iodine appears, dry and carefully wash off the iodine by floating over it a drop or two of chloroform, repeating until the spot is colorless. Let the residual spot dry, and add a drop or two of ammonia-water of about 10 per cent. strength—enough to leave free ammonia after action. A

¹ Morpholin has the structure, $HN \begin{matrix} \diagup CH_2 - CH_2 \diagdown \\ \diagdown CH_2 - CH_2 \diagup \end{matrix} O$. It is related to oxazin, $HN \begin{matrix} \diagup CH = CH \diagdown \\ \diagdown CH = CH \diagup \end{matrix} O$, and phenoxazin, $HN \begin{matrix} \diagup C_6H_4 \diagdown \\ \diagdown C_6H_4 \diagup \end{matrix} O$, the latter being the nucleus of well-known blue and violet coal-tar colors of determined constitution (see Guareschi's *Alkaloide*, Kunze-Krause, Berlin, 1896; Knorr, *On Morpholin as a Synthetic Product*, Pharm. Centralbl., 1897). See also Tamura, Mitt. a. d. med. Fak. d. kais. Univ., Tokio, 1919, xxii, 121; Kollo, Bull. soc. chim. România, 1919, i, 3 (Chemical Abstracts, 1920, xiv, 1674).

² Chastaing and Barillot, Compt. rend., 1888, cv, 941, 1012; Jour. Chem. Soc., 1888, liv, 165; further, Brown, Chemical Bibliography of Morphin, Pharm. Arch., 1898, i, 17, 25, 49, 54.

mahogany color indicates morphin,¹ the color being that of morphin oxidation products. The decanted chloroform solution (itself showing an iodine color if the morphin has been in considerable quantity) may be evaporated for the other test, to the residue a drop of very dilute starch paste being added, when free iodine will be shown by a blue color in the starch.

This negative test may better be made first by itself, thus: To the residual spot on white porcelain add a drop of very dilute starch solution, evaporate to dryness, cool, moisten with the solution of iodic acid from the point of a glass rod, and wait for the blue color. Now, whether or not the blue color of iodized starch be obtained, the positive test may be made at this point by adding a drop or two of ammonia-water, a slight excess, when the mahogany color, at once or after a few minutes, indicates morphin. This form of the test, with the disadvantage of the liberated iodine which has to be taken into colorless combination with sufficient ammonia, has, however, the advantage of avoiding the washing of the residue by chloroform with possible waste of material. Lefort recommends the application of the test as follows: Narrow strips of filter-paper are wet with a concentrated solution of the extracted matter to be tested, the strips dried and wet again several times. The dried strip is then moistened with the solution of iodic acid, partly dried, and then moistened with ammonia-water enough to leave a slight excess of the latter. The mahogany color, extending in the paper as far as it was wet at first, is an evidence of morphin and is quite permanent.

The liberation of iodine from iodic acid is effected promptly by many reducing agents, such as extractive matters from animal tissues or from medicinal drugs, many inorganic compounds, etc. As a reaction of morphin it is highly delicate, so that when the proportions of iodic acid to starch are right, a distinct starch color can be obtained from 0.01 mg.—according to Dupré, from 0.0065 mg. The right proportions of iodic acid and starch should be adjusted by a control test upon morphin, otherwise the test may fail of its full delicacy or even fail altogether.

The test by iodic acid with ammonia (Lefort's test) is distinctive of morphin so far as a single color-reaction can be relied upon. In the laboratory of Prescott the application of this test to numerous extracts from various orders of putrefied animal matter, by different modes of extraction, in no case gave a fallacious indication. The delicacy of this test nearly equals that of Fröhde's test. Davoll found that $\frac{1}{8400}$ grain (0.00001 gm.) of pure morphin would respond unmistakably to the Lefort test, but in the presence of such foreign matter as is almost unavoidable in extraction from tissues or foods he would not claim to recognize less than $\frac{1}{1280}$ grain (0.00005 gm.).² It is, therefore, some-

¹ J. Lefort, *Jour. Pharm. et de Chim.*, Paris, 1861, xl, 97; *Zeitschr. anal. Chem.*, 1862, i, 134; A. Dupré, *Chem. News*, 1863, viii, 267; D. L. Davoll, *Jour. Amer. Chem. Soc.*, 1894, xvi, 806. Lefort's entire article Upon Forensic Examination for Morphin is most valuable.

² *Jour. Amer. Chem. Soc.*, 1894, xvi, 807.

what less delicate than the iodic-acid-and-starch test, and the latter has a further practical advantage, in its negative bearing, that the blue is in contrast with common colors of extractive matters.

2. **The Test by Ferric Chlorid.**¹—For this test the material is best taken in the solid state; a fragment of it, or residue by evaporation of two or three drops of solution several times on the same spot, always on white porcelain, is moistened, from the point of a glass rod, with neutral ferric chlorid solution (1 : 15 or 20). There should be no free acid in the reagent, and it should not be basal enough to be at all turbid. With morphin or its salts a blue color is obtained—a somewhat permanent color—with excess of the reagent becoming greenish-blue (see Plate 5, No. 4). This color is destroyed by free acid, by heat, or by contact with alcohol. This is one of the least delicate of the tests for morphin. As a reaction it involves the formation of ferrous salts and of oxidation products of morphin, but it is likely that the main color product is a phenolic compound² of the unreduced ferric base, being merely a group reaction for the presence of free hydroxyl in the morphin molecule. Among alkaloids of ordinary occurrence this color-test is distinctive.³ Great numbers of aromatic compounds having phenolic hydroxyl in their structure give with ferric salts a blue or partly blue color; the homologous phenols, gallic acid, and tannins (the iron-tannin inks), salicylic acid, and wintergreen oil giving like color.⁴ The blue color produced by morphin with ferric chlorid is changed to orange fading to yellow by nitric acid, and the same orange changing to yellow is developed upon treating the alkaloid initially with nitric acid.

As for putrefaction products, Prescott stated that in great numbers of tests of the extracts of putrefied tissue to which he applied the ferric chlorid test he did not obtain therewith the morphin reaction, except in analyses when the presence of morphin was otherwise established beyond question. Even when morphin had been added by the chemist, as in the control analyses of Davoll (p. 433) and Smith (p. 434), the quantity of the morphin in the putrefactive matter used was not usually large enough to respond to this test, owing to its lesser delicacy.

The test by ferric chlorid and ferricyanid of potassium (essentially different from the test by ferric chlorid alone) is merely a reaction of reduction by morphin, the chief or only blue product being ferrous ferricyanid or ferric ferrocyanid or both. These products, containing no morphin derivative, are given by any reducing agent of sufficient intensity. The extracts from putrefied animal matter, as prepared in any of the tests for alkaloids, in many cases, perhaps in most cases, will respond to this test.⁵ In delicacy or sensitiveness the test far

¹ Pelletier, *Ann. de Chim.*, 1832, Ser. 2, 1, 240; *Ibid.*, 1836, lxi, 135.

² See p. 528.

³ Pseudomorphin, said to give this test, according to Hesse, is the same as oxydimorphin, the most ready oxidation product of morphin; further, as to the structure of oxydimorphin, see Danckwortt. *Arch. Pharm.*, 1891, cxxviii, 572, who claims that this compound contains the four hydroxyls of two molecules of morphin intact.

⁴ See Prescott's *Organic Analysis*, p. 399.

⁵ See Rosenbloom and Mills, *Jour. Biol. Chem.*, 1913, xvi, 327.

surpasses that by ferric chlorid alone. Consequently the test by ferric salt and ferricyanid has a negative value—to establish the absence of morphin (other reducing agents being excluded). Flückiger directs¹ that the reagent be prepared by dissolving 1 grain (0.065 gm.) of potassium ferricyanid in $6\frac{7}{10}$ fluidounces (200 c.c.) of water and 16 minims (1 c.c.) of ferric chlorid solution of specific gravity 1.281 (447 grains—29 gm.—in 2 fluidounces—59 c.c.—of water).

3. **Molybdic Test of Fröhde.**²—This is a changing color-test in which morphin is oxidized and molybdic acid reduced.³ “Fröhde’s reagent” is a freshly made solution of 1 or 2 milligrams (not over 5) of molybdic acid in 1 c.c. of concentrated sulphuric acid (strictly pure). Other directions specify higher proportions of the molybdic acid, but these lessen the distinctiveness of the test. In dissolving, heat above gentle warmth should not be employed. Alkali molybdate may be taken instead of molybdic acid, as in Buckingham’s modification.

The test must be applied to dry material, a particle of which, or the residue of a few drops of solution, on white porcelain, is treated in the cold with one drop of the freshly made reagent. Morphin and oxydimorphin give a deep purple color fading to violet and becoming green changing while under observation. If the mixture be allowed to stand, the greenish color will slowly change to yellow and, finally, to faint pink. These changes are the more rapid the less the amount of morphin. If the quantity of morphin be large, the violet color may persist for a long time. This reaction is quite distinct with pure morphin, but, as the residues obtained in toxicologic examinations are not always of the highest purity, one should be guarded in his deductions from this test alone. The result is always to be compared with that of a control test with known morphin.

Fröhde’s reagent gives bluish colors with codein and narcein; greenish colorations with apomorphin, berberin, emetin (turned blue by hydrochloric acid), and quinin (pale); reddish shades with brucin, emetin (changing to green), and veratrin; yellowish tints with aconitin, colchicin, and piperin. With salicin, a violet to cherry red; with phloridzin, a slow-forming blue; with colocynthin, a cherry red. The extracts of putrefied flesh, as prepared in different ways for alkaloid analysis under Prescott’s observation (when free from morphin), seldom, if ever, gave a blue color in this test. In the work of Smith (see p. 434) with anaërobic putrefaction, the final residue by the described method of extraction then employed, and, indeed, the final residue by Kippenberger’s method, gave no blue color at all under Fröhde’s test, except in the portion to which morphin had been added, and here, after the recommended extraction, a clear morphin reaction was obtained. In

¹ Reactions, Nagelvoort’s edition, Detroit, 1893, p. 76.

² Fröhde, Arch. der Pharm., 1866, clxxvi, 54; Almén, Upsala Läkareför., 1868, iii, 315; Kauzmann, Dissert., Dorpat., 1868; Neubauer, Ztschr. f. Russland, 1870, 661; Dragendorff, Organische Gifte, 1872; Prescott, Amer. Jour. Pharm., 1876, xlviii, 59; Flückiger’s Reactions, Nagelvoort’s edition, 1893, p. 75.

³ The play of colors obtained by action of morphin upon the molybdic acid, under the anhydration of the sulphuric acid, is so characteristic of a very few organic compounds that it must be due to formation of organic derivatives.

an investigation by Vaughan the extracts obtained by Dragendorff's method from anaërobic putrefaction of animal matters gave blue colors in Fröhde's test, alike in those portions to which morphin had and those to which it had not been added. In the work of Wormley,¹ in the analytic recovery of morphin from the urine of opium patients, from the blood, and from fresh organs of animals, with extraction mainly by amyl alcohol, he depended especially upon the test by Fröhde's reagent. Rosenbloom and Mills² show that putrefactive substances do not interfere with this test for morphin, as they could not obtain Fröhde's or other morphin reactions with decomposed material (either of aërobic or anaërobic origin) unless morphin was added to such material and, in the latter case, the results were unequivocal for the presence of morphin.

The sensitiveness of the molybdic and sulphuric acid test enables $\frac{1}{8466}$ grain (0.00001 gm.) of morphin, even when slightly contaminated with extractive matter, to give a decisive reaction.

4. **Other oxidizing agents in concentrated sulphuric acid**³ have been used in color-tests for morphin. Titanic acid, instead of the molybdic acid, gives a pink-violet to a brown-red color. Sulphuric acid containing selenious acid or ammonium selenite (Lafon's reagent 1 gm. in 20 c.c. H_2SO_4 , or Mecke's reagent, 0.005 gm. of selenious acid per mil. of H_2SO_4) gives with morphin a blue, changing to green, and then to brown; while such a reagent produces, with codein, heroin, and apomorphin a preliminary green, changing to blue, and then to a grass green. Concentrated sulphuric acid alone and cold, when free from traces of nitric acid, gives no color to morphin free from traces of other opium alkaloids. On warming by the water-bath, purple to brown colors are developed.

In *Pellagri's test*⁴ the portion is first dissolved in fuming hydrochloric acid, then concentrated sulphuric acid is added, and the mixture is evaporated on an oil-bath at 100° to 120° C. (212° to 248° F.). The presence of morphin (codein, apomorphin, or heroin) is shown by a purple color at the edges, and after evaporation of all the hydrochloric acid, a red color. Dissolved again in hydrochloric acid it becomes violet when neutralized with sodium bicarbonate. If hydriodic acid or dilute alcoholic solution of iodine is added, the color changes to green and becomes soluble in ether, which it tints purple.

In another test, the *Husemann's modification of the Erdmann's reaction*,⁵ if the solid material be moistened with pure concentrated sulphuric acid and either allowed to stand for twenty-four hours in a desiccator or placed in an air-bath at 100° to 105° C. (212° to 221° F.) for five or ten minutes, a slight reddish or brownish color may appear. If the mixture

¹ Wormley, Univ. Med. Mag., 1890, ii, 399; Chem. News, 1890, lxii, 65, 79 and 99.

² Jour. Biol. Chem., 1913, xvi, 327; see also Rosenbloom, Ibid., 1914., xviii, 131.

³ Prescott, Amer. Jour. Pharm., 1876, xlviii, 62; Vulpis, Pharm. Centralhalle, 1891, xxxii, 231.

⁴ G. Pellagri, Gaz. chim. ital., 1877, vii, 297; Jour. Chem. Soc., 1877, xxxii, 808.

⁵ Ann. der Chem. und Pharm., 1863, cxxviii, 305; see also Hankin and Chatterji, Analyst, 1920, xlv, 171.

⁶ Ibid., 1861, cxx, 188.

has been heated, allow the dish to cool and add 1 or 2 drops of concentrated nitric acid (or a crystal of potassium nitrate or chlorate), when a reddish-violet color appears, soon changing to blood red and then yellowish red. If the nitric acid be added to a freshly prepared and unheated mixture of morphin and sulphuric acid, a rose-red color is obtained which soon changes to yellow. Oxydimorphin, apomorphin, codein, and heroin show the same results with this test as does morphin. Its limit of delicacy is about 1 : 40,000. Nitric acid alone colors morphin an orange red to deep red color changing to yellow. This latter color is not restored to red on addition of stannous chlorid or of ammonium sulphid as is that produced by brucin.

Cane-sugar and *sulphuric acid* are used in a very delicate morphin test as follows: The residue to be tested is evaporated with from two to eight times as much cane-sugar; and to the dry residue, when cold, a drop of concentrated sulphuric acid is added, the reaction giving a purple color changing to blood red and fading with other colors. Under similar conditions, oxydimorphin is colored green, while codein reacts like morphin. Uranium acetate gives a reddish-brown color, and on further addition of alkalis, a deep-red precipitate (Lamal).¹

5. The Marquis Test.—The reagent for this test² consists of 3 c.c. of concentrated sulphuric acid to which 2 drops of 40 per cent. formaldehyd (formalin) have been added. If the dry residue or material to be tested for morphin, on white porcelain, is touched from the point of a glass rod with this reagent, an intense purple-red color, changing to violet, and finally to blue is obtained. This reaction is quite distinctive, and is regarded by Kobert as the best at our disposal. A marked reaction is obtained with 0.02 mg. The alkaloids related to morphin show somewhat similar reactions with this test, although the colors are slightly different. Thus codein and apomorphin do not give the initial purple, but strike a violet changing to blue; oxydimorphin shows a green color, which changes to a flame red; dionin gives a dark blue violet; while heroin shows the same colorations as does morphin. Gauss³ has devised a colorimetric method with this reagent for the estimation of morphin.

6. Denigés' Tests.—Place in a test-tube 10 c.c. of dilute solution of the residue (the lower limit of concentration being 0.03 gram per liter), add 1 c.c. of hydrogen peroxid and 1 c.c. of ammonium hydroxid solution and, then, 1 drop of a 4 per cent. solution of copper sulphate. Shake the mixture. At once a rose red to a deep red color appears, depending on the concentration of the alkaloid present. Positive results are not obtained with codein, thebain, papaverin, narcein, or narcotin; while oxydimorphin, apomorphin, heroin, and dionin give somewhat similar results.⁴

¹ Jour. Chem. Soc., 1895, lxviii, pt. ii, 375; Sem. méd., 1894, xiv, 267.

² Dissert. Dorpat., 1896; Arbeit. der pharm. Inst. zu Dorpat., 1896, xiv, 117; see also Istrati, Bul. Soc. Sciinte din Bucuresei, 1898, vii, 168; Prescott, Pharm. Arch., 1901, iv, 89; Jour. Soc. Chem. Ind., 1898, xvii, 954; Kobert, Apoth. Ztg., 1899, xxxvii, 259; Heiduschka and Faul, Arch. der Pharm., 1917, 254, 171.

³ Jour. Lab. and Clin. Med., 1921, 6, 699.

⁴ Compt. rend. Acad. des Sci., Paris, 1910, cli, 1062; see also Ganassini, Boll. Chim. farm., 1921, 60, 2.

Oliver¹ has modified this test slightly as follows: To a few cubic centimeter of the aqueous or slightly acidulated solution of the suspected extract add 1 c.c. of hydrogen peroxid and 1 c.c. of ammonia. Stir the mixture with a piece of clean copper wire, when the previously colorless solution will assume a deep port wine color if morphin be present, the reaction being accompanied by a considerable evolution of gas. By this reaction 0.00002 gram of morphin is readily detected. If the amount of morphin be very small, it is necessary to add a few drops of potassium cyanid solution at the end of the reaction to remove any blue color formed from the copper itself. This cyanid solution should not be added before the mixture is stirred with the copper wire, as the reaction will not appear if this be done. Codein, narcotin, heroin, and dionin fail to give this reaction, according to Oliver, but one of us (Webster) has obtained deep shades of red with both heroin and dionin. Apomorphin strikes an orange color with this test. Negative results are shown with strychnin, brucin, atropin, cocain, nicotin, emetin, veratrin, physostigmin, pilocarpin, and coniin.

Denigés has recently introduced a further test for morphin, which depends upon the conversion of this alkaloid into apomorphin. It has been known for some time that apomorphin solutions assume a blue color when shaken with alkali in the air. Grimbart and Leclère² have shown that this color may be more rapidly and intensely produced by boiling an apomorphin solution with sodium acetate in presence of bichlorid of mercury. Denigés³ extends this reaction to morphin as follows: Heat a few milligrams of morphin with 2 or 3 drops of concentrated sulphuric acid in order to convert the morphin into apomorphin. Now dilute this solution with 5 c.c. saturated solution of sodium acetate and 2 drops of 4 or 5 per cent. solution of mercuric chlorid and boil. In the presence of morphin a deep greenish-blue color appears. This reaction is also given by codein, heroin, and dionin.

7. Lautenschlaeger's Diazonium Test.—The basis of this test⁴ is the fact that morphin, in the presence of alkalis, forms dyestuffs with diazonium compounds. The reagent is a solution of diazotized sulphanilic acid prepared as follows: Dissolve 0.2 gram of sulphanilic acid in 80 c.c. of distilled water, cooling with ice if necessary. Add 10 c.c. of N/10 hydrochloric acid and 10 c.c. of N/10 sodium nitrite solution.

Dissolve a portion of the residue obtained in the extraction processes in a little dilute sulphuric acid. Render this solution alkaline with sodium carbonate or bicarbonate, and add an equal volume of the above diazonium reagent. A red color, changing to orange on addition of acid, immediately appears. The reaction is sensitive in a dilution of 1 : 10,000 (faint red); with a dilution of 1 : 1,000,000 the color is distinctly yellow; while with a dilution of 1 : 2000 a thin layer is intensely dark red. No opium alkaloid other than morphin reacts as above; the same thing is true of the synthetic derivatives dionin, heroin, and peronin. Of other alkaloids yielding color reactions with diazo compounds in alkaline

¹ Med. Chron., 1914, xxvii, 221.

³ Ibid., 1919, xix, 49.

² Jour. pharm. chim., 1915, xi, 23.

⁴ Arch. der Pharm., 1919, cclvii, 13.

solutions may be mentioned emetin (red), spartein (yellow), physostigmin (red), coniin (bright yellow), and nicotin (bright yellow). Of these colors, only that of morphin is stable in acid solution.

8. The general precipitating reagents—iodin with potassium iodid, potassium mercuric iodid,¹ potassium bismuth iodid, phosphomolybdic acid, etc.—give quite complete precipitation with morphin. The precipitate by phosphomolybdate dissolves in ammonia with a blue color. The precipitate by fixed alkalis is freely redissolved by their excess; that by ammonia is but slightly redissolved.

9. **The Identification of Morphin Crystals.**—For this purpose the free alkaloid is preferable to its salts, and alcohol of about 95 per cent. is the more favorable solvent. Solution in ammonia-water has been employed, but is not to be recommended. In rapid crystallization, such as occurs in cooling a warm alcohol solution, only needles are obtained—not distinctive. The crystallization should be slow enough to give columns whose end-surfaces will clearly show their boundary-lines.² To retard or even prevent altogether the evaporation of the



Fig. 54.—Morphin crystals from alcohol.

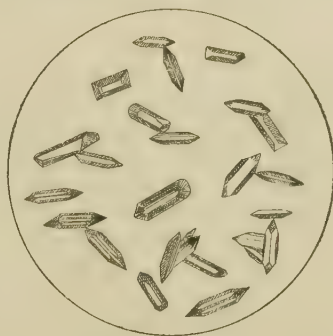


Fig. 55.—Morphin crystals from ammonia solution.

alcohol solution it may be dropped upon a watch-glass, which is then covered with another watch-glass. It serves better still to place the solution on a watch-glass or a glass slide, under a small bell-jar, and place also underneath a small roll of filter-paper wet with alcohol. To obtain crystals from a minute amount of morphin, such as that extracted from tissues or other mixtures, a final residue of such extractions is treated with warm alcohol, in repeated portions of only a drop or two, and the solution, concentrated if need be, is drained into a cavity four or five millimeters wide on a glass surface. A suitable receptacle is made by a section of glass tubing cemented upon a glass slide with a little paraffin. From time to time the result may be observed under a power of 50 diameters, which is suitable for the full examination of crystals. Morphin crystallizes in columns, single and grouped, of the orthorhombic system, with hexagonal end-surfaces. The crystals begin

¹ See Koller (Schweiz. Apoth. Ztg., 1920, lviii, 330) for a microchemical test with this reagent, giving yellow star- or broom-shaped or spherocrystals.

² See Wherry and Yanovsky, Jour. Wash. Acad. Sci., 1919, ix, 505.

to lose their crystallization water (one molecule) at 75° C. (167° F.); more rapidly at from 100° to 120° C. (212° to 248° F.). The alkaloid blackens before melting and melts at about 230° C. (446° F.). In the subliming cell the upper disk was clouded at 150° C. (302° F.).¹

The chemist cannot be assured that any crystalline forms are those of morphin unless they are found to respond to the chemical tests for this alkaloid. These tests may be applied to a minute crystal under a good hand-magnifier. All chemical indications gain additional force when obtained from the crystals, however minute.

Biologic Test for Morphin.—It has been found by Straub and Herrmann² that white mice show a relatively characteristic response to injection of morphin or its salts. If a neutral or slightly alkaline (not acid) solution of morphin hydrochlorid be injected under the skin of the back of a white mouse weighing about 16 to 20 grams (small mice of about 5 grams weight are not suitable) the following symptoms are noted: the back of the animal assumes a lordotic curvature; the hind legs show a slight spastic paralysis, being more markedly stretched out than usual; movements of the animal appear difficult; the tail of the animal raises up in a characteristic S-shaped curvature, finally lying over the back of the animal with the tip being over the ear; the whole behavior of the mouse gives the impression of increased restlessness and stimulability, so that it springs into the air in response to slight noises, especially those of high pitch. The position of the tail is the most characteristic part of the reaction, the curvature remaining more or less constant for many minutes or hours, although the maximal curvature is never constant but shows stronger curves from time to time in response to outside stimuli. There appears to be a direct relation between the continuance of the reaction and the amount of morphin injected. Thus, with a dose of 5 mg. the reaction continues about twenty hours, while with a dosage of 0.005 mg. it continues for forty-five minutes. Likewise, the maximal reaction is related to the dosage of the drug. Thus with a dose of 5 mg. the maximum response continues for four and a half hours, while with a dosage of 0.01 mg. this is thirty to forty-five minutes. The lower boundary of dosage necessary to provoke this reaction appears to be 0.01 mg., although some animals do not react to less than 0.02 mg.

Papaverin, narcotin, narcein, thebain, and ethylmorphin show this reaction somewhat irregularly and, even then, only in response to much larger doses than are necessary with morphin. Codein, apomorphin, and heroin show similar reactions to morphin, but with the first two of these drugs the amount required to produce the reaction is 0.1 mg., while with heroin the response is shown by doses lower than in the case of morphin, namely, with 0.005 mg. Hence it would appear necessary that heroin be excluded by other tests or by the history of the case. Nicotin produces catatonic phenomena when injected into frogs, but

¹ Blyth, *Poisons: Their Effects and Detection*, London, 1906, 260.

² *Biochem. Ztschr.*, 1912, xxxix, 216; see also Kaufmann-Asser, *Ibid.*, 1913, liv, 161; Heinekamp, *Jour. Pharm. and Exp. Therap.*, 1922, xx, 107.

the response to this test is not elicited by doses of nicotin in any such quantity as are necessary with morphin; in other words, the response with nicotin is about fifty times as weak as with morphin. Strychnin causes fatal tetanic convulsions in doses of 0.03 mg., smaller doses of this drug producing no reactions similar to those given by morphin. Atropin shows no reaction. Raspers¹ has shown that cocain, caffen, diuretin, and camphor produce similar reactions when injected into a mouse, but the amounts necessary to produce the results are far in excess of those in the case of morphin. Very small doses of picrotoxin, tetanus toxin, or of potassium oxycyanid produce this reaction, but these would hardly come into consideration in the examination of residues for morphin.

From the medicolegal standpoint this test is hardly sufficiently distinctive, by itself, to warrant a definite statement of the presence of morphin in an extract. It is, however, of value as a confirmatory test and, also, as a preliminary procedure in the examination of the extracts, as it is not absolutely necessary that the Stas-Otto or Dragendorff process be carried further than the first stage of separation to permit of the test being applied.

The Separation of Morphin from Animal Tissues.²—The finely divided material, in a weighed portion, is taken in a flask having a return-condenser, covered with diluted alcohol (of about 50 per cent. by volume), distinctly acidulated with acetic acid,³ and the contents digested in the closed flask at about 70° C. (158° F.) for one hour, when the whole is cooled, strained, the residue washed with a little of the dilute acidulated alcohol, and returned to the flask. On the residue the digestion and straining are repeated a second and a third time. The mixed alcoholic filtrates and washings are evaporated on the water-bath to a syrupy liquid; to this is added three times its volume of very slightly acidulated (acetic) alcohol of 95 per cent., and the whole in a containing flask is corked and shaken and set aside for from twelve to eighteen hours, agitating from time to time.

The mixture is then filtered, using a filter-pump—better with a Büchner funnel—and the residue washed with successive small portions of alcohol of the same alcoholic strength and acidulation as the filtrate. All alcohol is now evaporated off at water-bath temperature. Water just perceptibly acidulated with sulphuric acid is now added in quantity barely enough to bring the soluble matter into limpid solution, the whole well stirred, and the insoluble matters filtered out. The filtrate, which must be filtered clear, is now to be shaken out with the immiscible solvents as follows: (1) While acid, with chloroform in several small suc-

¹ Arch. neerland. de physiol., 1916, i, 71; Chem. Abs., 1917, xi, 2913.

² This method, as here specified, is but slightly different from that given by Davoll (Jour. Amer. Chem. Soc., 1894, xvi, 802) from work done in the chemical laboratory of the University of Michigan. It was also the method used by H. T. Smith, as cited on p. 434. As regards general methods of separation of alkaloids from tissues see p. 52 et seq., in section on General Principles of Toxicology.

³ Tingle (Amer. Jour. Pharm., 1918, xc, 689, 788 and 851) advises the use of hydrochloric or salicylic acid to prevent the possibility of conversion of a portion of the morphin to apomorphin.

cessive portions; (2) on making the liquid alkaline with ammonia, with four small portions of a mixture of chloroform and ether (3 : 1), acidulating and making alkaline before each portion of the immiscible solvent is used¹; (3) after slight acidulation and warming, with hot amyl alcohol in several portions; (4) after making alkaline with ammonia and warming with hot amyl alcohol² as the solvent for morphin, this being applied in repeated portions. The immiscible solutions, (1), (2), and (3), being respectively chloroform, chloroform-ether, and amyl alcohol, should be once or twice shaken out with a small quantity of acidulated water, and these small water-washings should be added to the aqueous liquid treated in (4). The final morphin extraction in (4) is made with liquid and solvent both hot, and continued in at least three successive portions, and until on evaporating 1 or 2 c.c. a negative result is obtained with one of the more delicate tests. The united amyl alcohol solutions are filtered (first wetting the filter with amyl alcohol), cooled, and shaken out with water in very small portions until the resulting washings give no precipitate with barium chlorid. The amyl alcohol solution, so washed, is measured and held in reserve for qualitative and, if need be, quantitative determinations, each made upon an observed volume. Autenrieth³ recommends the extraction of morphin from ammoniacal solutions with hot chloroform, several extractions being necessary. If this chloroform residue is too impure, as evidenced by a red or brown color, it must be purified as follows: Dissolve it in hot amyl alcohol and shake the solution thoroughly with several portions of hot water containing a few drops of dilute sulphuric acid. The acid dissolves the morphin, whereas the amyl alcohol retains most of the coloring-matter. Add ammonium hydroxid solution in excess to the acid solution and extract several times with hot chloroform. Morgulis and Levine⁴ employ chloroform for extracting the morphin directly from the evaporated alkalinized morphin tartrate solution, no shaking out process being used. Kippenberger⁵ advises the use of chloroform containing 10 per cent. of alcohol by volume as a solvent for morphin, while Williams⁶ and Tingle⁷ advocate a mixture of 2 volumes of chloroform and 1 volume of alcohol.

Portions may be evaporated to dryness for color-tests, and other portions may be shaken out with a little acidulated water for tests by

¹ The purpose of this solvent is to remove cadaveric alkaloids. In shaking out with each portion the liquid is just acidulated, the immiscible solvent shaken in, then the liquid made perceptibly alkaline, and the mixture at once sufficiently shaken. Generally the shaking-out with an immiscible solvent should be repeated until, after shaking out, a few drops upon evaporation on glass leave no more residue than that resulting from the slight miscibility of the aqueous solution itself.

² The amyl alcohol especially should be rectified by redistillation if necessary until the residue of an evaporated portion gives no interfering tests.

³ Detection of Poisons, Amer. ed., 1915, 125.

⁴ Jour. Lab. and Clin. Med., 1920, v, 321.

⁵ Ztschr. f. anal. Chem., 1900, xxxix, 201 and 290; see also Puckner, Jour. Amer. Chem. Soc., 1901, xxiii, 470.

⁶ Amer. Jour. Pharm., 1914, lxxxvi, 308.

⁷ Ibid., 1918, xc, 689, 788, and 851; see also Wachtel, Biochem. Ztschr., 1921, 120, 265.

precipitation. It is well to note the volume of each portion taken, in known ratio to the volume of the whole, and it saves time to have the entire or a given part of the amyl solution concentrated to an observed volume. For color-tests a known quantity is evaporated upon the space of a drop or two on white porcelain, dropping the solution in tenths of a cubic centimeter from a pipet only so fast as it dries over the water-bath, and again and again in the same place. Another and a considerable fraction may be evaporated upon glass, taken up in ethyl alcohol, and cooled to crystallize.

If estimation of quantity is to be made, let as large an aliquot part of the amyl solution as is available be evaporated to dryness. In this the morphin may be estimated by the following method: Carefully dissolve all the morphin in the residue by treatment with a very slight excess of dilute acetic acid. Wash and add water to a given volume—say 5 c.c. Take 10 c.c. (or a volume twice that of the morphin solution) of a standard solution of iodine with iodide of potassium, about decinormal in strength (1.2692 gm. free iodine and 1.8 gm. potassium iodide in 100 c.c.). To this volume of the iodine solution, while shaking, slowly add the measured solution of morphin, add water to make the mixture about five times that of the iodine solution, and shake until the supernatant liquid is perfectly clear or transparent. Take the exact volume of the mixture, filter off just half of this volume (representing exactly half of the iodine solution taken), and titrate with a standard solution of thiosulphate to estimate the free iodine. In this way find the weight of iodine consumed in precipitating the alkaloid, and multiply by 0.74918 and by 2, when the product will be the weight of anhydrous morphin in the entire morphin solution precipitated. The precipitate is $C_{17}H_{19}NO_3 \cdot HI \cdot I_3$. Then $31 : C_{17}H_{19}NO_3 :: 1.0 : 0.74918$.¹

This method may also be employed in the estimation of the morphin in mixtures which may have been taken with poisonous effects.

Instead of using the above method, one may employ the acidimetric titration process as follows: Dissolve the dried residue from the evaporation of the amyl alcohol solution in a known amount of N/10 sulphuric acid solution. Titrate the excess of acid with N/50 potassium or sodium hydroxide solution, using cochineal as an indicator. Each cubic centimeter of N/10 sulphuric acid consumed in the combination with morphin in the residue corresponds to 0.028516 gram of anhydrous morphin.²

As to the factor of inevitable waste of this alkaloid in extraction from tissue-substances, foods, or medicines, it is best determined by a control analysis, carried with material as nearly as possible the same as that of the real analysis undertaken (see p. 432).³

¹ This method corresponds with that reported by Gordin and Prescott, Jour. Amer. Chem. Soc., 1898, xx, 728.

² See Gauss (Jour. Lab. and Clin. Med., 1921, 6, 699) for a colorimetric method based upon the use of Marquis' reagent.

³ See also the article of Davoll, Jour. Amer. Chem. Soc., 1894, xvi, 799. In this article, by inadvertence in the calculation of weight of morphin into that of morphin sulphate (p. 799, A, B, C), the figure for the sulphate is given at twice the true figure.

Morphin-like Ptomains.—In some notable trials for murder question has been raised concerning the validity of certain color-reactions obtained and supposed to indicate the presence of morphin. This confusion has arisen, owing to the fact that certain products of bacterial action have been isolated which show some similarity with some of the tests for morphin. While it is undoubtedly true that many basic products of more or less toxicity are produced by bacterial activity, yet it is quite as true that these derivatives do not show exactly the same chemical or color reactions, identical in all respects, as those given by the vegetable alkaloids. Perhaps one should make an exception of such putrefactive products as pyridin, pyrrol, indol, phenol, etc., inasmuch as these bodies might be the cause of a true exogenous poisoning and, at the same time, be detected in the cadaver as putrefactive endogenous products. Such cadaveric substances do not, however, come into consideration in the detection of morphin, providing proper precautions are taken to exclude them by careful methods of extraction and, especially, if insistence be made that the color reactions shall coincide in every detail with those given by known specimens of morphin. It would seem self-evident that morphin may be safely stated to be present if the reactions previously discussed be shown by a purified residue in the same color tones and the same sequence as shown by known morphin. In none of the cases, in which question has arisen, have these reactions been identical in every respect, although there has been similarity, but this is not sufficient to warrant conclusions. Exact duplication of the results with the unknown and known substances must obtain. No ptomains have been discovered, or at least reported, that show all the color reactions of morphin in exact color tones or sequence of colors, as compared with those given by known morphin. The most important cases reported, in which confusion arose as to the identity of a residue isolated from human bodies, are the following:

In the Songzogna trial at Cremona, Italy, in 1873, the experts seem to have confounded a basic putrefactive substance with morphin. This substance was not removed from either alkaline or acid solutions with ether, but could be extracted with amylic alcohol. It reduced iodic acid, but in its other reactions, as well as in its physiologic properties, it bore no resemblance to morphin. It failed to give both the ferric chlorid and the Pellagri test for morphin. In the same body there was found a substance that was extracted from alkaline solutions with ether, and that gave, with hydrochloric acid and a few drops of sulphuric acid on the application of heat, a reddish residue similar to that obtained by the same reagent with codein, but in its other reactions it did not resemble this alkaloid. While the experts in this case asserted the presence of morphin on the above evidence, it is clear, as Selmi. showed at the time, that the substance isolated was not morphin¹ This case indicates the necessity of the insistence that all the reactions

¹ Sulle Ptomaine, Bologna, 1878, 67 et seq.

for morphin be obtained in a manner which is unequivocally identical with those given by known morphin.

In the case of Urbino de Freitas,¹ which occurred in Portugal in 1893 the experts for the prosecution reported the presence of morphin, narcein, and delphinin in the tissues. They relied for their evidence as to the presence of morphin upon the iodic acid reaction, the test with Fröhde's reagent, the test with Lafon's reagent (a solution of 1 gm. of ammonium selenite in 20 c.c. of concentrated sulphuric acid), and the evidence of alkaloids in the residue obtained by the use of the general alkaloidal reagents. There is probably little question that these experts made the mistake of asserting the presence of morphin on insufficient data, as the Fröhde test was not characteristic, the iodic acid reaction is given by many other substances, and the reactions of Lafon's reagent with various alkaloids were not well known at that period. The experts for the defense offered the following criticisms: (1) The chemical examination of the viscera was made at a time when putrefaction was well advanced; (2) amyl alcohol was used in extracting the alkaloids; and, moreover, the amyl alcohol was not pure but contained many basic substances and possibly furfural; (3) the method used by the prosecution in detecting the presence of morphin and narcein in the urine was defective; (4) the physiologic results obtained with the syrupy extracts did not show the presence of vegetable poison, and (5) the color reactions obtained for the alkaloids mentioned were not sufficient to enable one to make a positive statement concerning their presence. The controversy between the experts on the two sides of this case finally involved most of the prominent toxicologists of Europe, inasmuch as the evidence was submitted and testimony obtained from them. While many of the experts (as for instance, Husemann, Dragendorff, Stephenson, and Lewin) believed that it was certain that the Portugese experts mistook putrefactive products for vegetable alkaloids, it is to be noted that the results upon which these latter experts relied were in reality not sufficient to accord with our statement that the reactions of the unknown residue must correspond in exact detail with those shown by known morphin, a condition which did not obtain in this case as may be readily seen from a perusal of the evidence as introduced.

In the Buchanan case in New York, the symptoms as testified to by the attending physician clearly were not incompatible with those that might be due to disease. The chemists for the prosecution swore to the presence of morphin and atropin in the dead body. The test upon which they relied were the ordinary chemical reactions, and the question arose as to whether or not they were sufficiently distinctive. Vaughan² states that "all the tests obtained by the experts were duplicated with putrefactive alkaloids." These latter products were obtained by Vaughan³ by anaërobic putrefaction of 5 kilograms of ox liver finely

¹ Porto, 1893, 122 and 208 (cited by Witthaus).

² Vaughan and Novy, *Cellular Toxins*, 1902, 240.

³ *Trans. Assoc. Amer. Physic.*, 1894, ix, 249.

chopped and mixed with 2 grams of white arsenic (as the body in the Buchanan case had been emblamed with arsenic), the fermentation being allowed to continue for thirty days. One kilogram of this decomposed tissue was placed in each of three evaporating dishes, and these were marked A, B, and C. To B, 130 mg. of morphin sulphate was added, and to C the same amount of morphin sulphate together with 0.5 gram each of indol, skatol, and phenol. No addition was made to A. These separate portions were carried through all the manipulations recommended by Dragendorff in his process for the separation and recovery of morphin. The purified residues were submitted to the tests with the following results: With nitric acid, all became lemon yellow; with sulphuric acid, no change in any; with sulphuric and nitric, all became lemon yellow; with ferric chlorid, all became bluish green; with iodic acid, all promptly reduced the acid; with Fröhde's reagent, all became blue with a faint and evanescent purple in B and C; with Pellagri's test, all responded promptly. While these colorations are more or less similar to those produced with pure morphin, yet they are by no means identical, so that our insistence on identity of reaction still holds good. Rosenbloom and Mills¹ duplicated these tests, and conclude from their results as follows: "Bacterial products formed during aërobic and anaërobic putrefaction of certain human organs did not in any way give reactions simulating those due to the presence of morphin, and in no way interfered with the detection of morphin when morphin was added to these putrefactive products."

From this discussion it would appear that the analyst, while admitting the possibility of influences of the putrefactive bases upon the reactions for morphin, should take special precautions in the purification of his residues and reagents, and should make his identification tests side by side with specimens of known morphin. The reactions shown by these putrefactive bases vary in color or sequence of color from those given by the pure alkaloid in some one or more of its characteristic tests. Pseudoreactions must be eliminated and insistence laid upon unequivocal color and chemical reactions. If the residue corresponds in every detail with the sample of known morphin, then it appears to the writer that one is justified in stating that he is dealing with morphin and not with products of putrefactive origin.

Meconic Acid.—Existing in combination with morphin, in opium, and not known of any other source, the detection of this acid in analysis is important as proof of opium. If both morphin and meconic acid are found, the evidence of opium is complete.² Chemical tests for meconic acid are distinctive and delicate. As applied to the contents of the stomach, if opium or laudanum is retained in this organ, the tests for meconic acid offer a reasonable probability of its detection.

Detection.—The contents of the stomach, or other materials analyzed

¹ Jour. Biol. Chem., 1913-14, xvi, 327; Rosenbloom, *Ibid.*, 1914, xviii, 131.

² See Heiduschka and Faul, *Arch. der Pharm.*, 1917, cclv, 482; *Chem. Abs.*, 1920, xiv, 798.

for meconic acid, finely divided, are digested with water moderately acidulated with acetic acid, on the water-bath, for about an hour. The whole is then filtered, the filtrate evaporated to a concentrated solution, three or four volumes of strong alcohol slowly stirred in, and the precipitated matters filtered out and washed with alcohol of about the same strength as the filtrate. The alcohol should now be evaporated from the total filtrate, and the syrupy remainder dissolved in water slightly acidulated with acetic acid and filtered. To the filtered liquid lead acetate solution is added in slight excess. The precipitate, if obtained, is to be examined for the meconic acid as a lead salt. The filtrate and washings are treated with hydrogen sulphid to precipitate all the lead, which, after standing an hour or longer, is filtered out. The last filtrate, with washings, is evaporated to remove all the hydrogen sulphid, and treated, in analysis for morphin, as directed under the head of Separation from Tissues, after the stage of digestion with acetic acid. The precipitate to be examined for meconic acid is now suspended in a little water and treated with hydrogen sulphid gas and filtered to remove all the lead. The filtrate from the lead sulphid is well concentrated by evaporation, filtering to keep clear, and the final solution subjected to the tests for meconic acid. Ferric chlorid strikes a characteristic deep red or purplish-red color. The color is not readily destroyed by boiling nor by hydrochloric acid (difference from acetic acid), nor by addition of mercuric chlorid (difference from thiocyanic acid). This color is, however, destroyed by the addition of stannous chlorid, but the color returns on addition of nitrous acid. Lead acetate gives a yellowish-white precipitate of lead meconate, not easily dissolved by acetic acid, but colored red when touched by ferric chlorid. Meconic acid is dissolved out from acidulous watery solutions by ether. It is best crystallized in the cooling of a somewhat concentrated hot-water solution or from ordinary alcohol.

In examination for opium the **contents of the stomach** should always be carefully inspected, before chemical treatment, for fragments of the mass of opium. Filtered and washed portions of the sedimentary matters are to be searched by the aid of a hand-magnifier and a microscope with objective of about 50 diameters, comparing with residues of opium similarly treated. On first opening the stomach attention should be given to the odor, whether that of opium or laudanum can be distinguished.

The Deposition of Morphin in the Body.—Morphin is eliminated largely through the mucous membrane of the stomach and intestines, either unchanged or but slightly changed, and, according to the more



FIG. 56.—Crystals of meconic acid: a, From 95 per cent. alcohol; b, from water.

recent research, to a considerable extent through the urine. Its appearance in the alimentary canal as a result of its hypodermic injection is quite marked (see Cases 23 and 67 above). That morphin is, to a certain extent, gotten rid of by oxidation in the blood can hardly be doubted, as the alkalinity of the blood is conducive to the change. The exact products of this oxidation have not been determined, although oxydimorphin is unquestionably one of the early derivatives. Morphin has been found in the liver, gall-bladder, kidneys, brain, spleen, and blood, in addition to the stomach, intestines, and urine. If the diagnosis of morphin poisoning be in doubt, the urine should, by all means, be examined if it can be done in time; but, in view of certain of the work on this subject, it must be remembered that failure to find this poison in the urine should not be held as conclusive against its presence in the system.

Kobert¹ states that only small and varying quantities of morphin appear in the urine. Wormley² in examining the urine of 6 persons who had taken morphin found it present in all the cases, but in 4 no more than a distinct trace was obtained, the remaining 2 cases showing morphin in considerable quantities. Marquis,³ after injecting morphin into the circulation of a cat, found that the urine, large intestine, the stomach, and saliva together yielded 12 per cent. and the liver 30 per cent. of the alkaloid administered. Notta and Lugan⁴ found morphin constantly in the urine of persons taking this alkaloid habitually, and conclude that it is in these cases largely eliminated in the urine, and may be found when 0.1 gram or more are taken daily. On the other hand, Bornträger⁵ could not find any morphin in the urine of a person who took large doses daily by the mouth, but found it in the feces. On subcutaneous administration, in 1 person the urine showed traces of morphin even when it was given in very small doses; in another person, to whom much larger doses were administered, the urine showed no trace of the alkaloid. Landsberg⁶ concludes, from many experiments with dogs, that at most only traces of the morphin reach the urine of the dogs poisoned by it; that a part goes out in the feces and a part is decomposed in the alkaline blood. Tauber⁷ found after injection of morphin into the blood of a dog that he could recover it largely from the blood and a portion from the feces. Antheaume and Mouneyrat⁸ report the following: A man of forty-two years, a victim of the morphin habit, had formerly taken 62 grains (4 gm.) daily and more recently 2 grams daily, but had received no morphin for fourteen days, when he died. Morphin was found most largely in the liver,

¹ *Lehrbuch der Intoxicationen*, 1906, 971.

² *Univ. Med. Mag.*, 1890, ii, 399; *Chem. News*, 1890, lxii, 65, 79, and 99.

³ *Chem. Centralbl.*, 1897, lxxviii, 249; *Pharm. Centralhalle*, 1897, xxxvii, 844.

⁴ *Chem. Centralbl.*, 1885, 3 F., xvi, 967; *Jour. de pharm. et de chim.*, 1884, 5 s. x, 462; *Arch. der Pharm.*, 1885, 3 s., xxiii, 512.

⁵ *Ibid.*, 1880, xvii, 119.

⁶ *Pflüger's Arch.*, 1882, xxiii, 413; *Jour. Chem. Soc.*, 1882, xlii, 543.

⁷ *Arch. exp. Path. u. Pharm.*, 1890, xxvii, 335; *Chem. Centralbl.*, 1890, ii, 666.

⁸ *Compt. rend. Acad. des sc., Paris*, 1897, cxxiv, 1475.

also in the kidneys and the brain. Wormley,¹ in a few cases, recovered morphin from the blood of animals shortly after administration: "In no instance, however, were crystals obtained or were the results, with perhaps a single exception, such as would have been satisfactory in an unknown case." Later, however, he obtained by improved methods more uniform recovery from the blood. Faust² and Heffter³ believe that morphin is excreted in the urine in only very small amounts. Van Rijn⁴ reports that he recovered from the urine 35 per cent. of the morphin given to a rabbit, while Kaufmann-Asser⁵ obtained 39 per cent. of the morphin injected from the urine and showed its presence in the liver, kidneys, and stomach. Ipsen⁶ also calls attention to the importance of examination of the urine in cases of morphin poisoning. Homburger and Munch,⁷ using Autenrieth's modification of the Stas-Otto process with a five-hour extraction of the organs and three extractions with ether in both acid and alkaline solutions followed by a final extraction of morphin with hot amyl alcohol, showed that 97.5 per cent. of the morphin injected into cats and rabbits could be recovered if the analysis be started soon after death. The yields in these tests indicated the following order of accumulation of morphin in the system of the cat: urine, liver, kidney, spleen, and stomach. With the rabbit the amounts found were stored in the following order: kidney, liver, urine, spleen, and stomach. They believe that the loss of morphin from a cadaver proceeds in two stages: a preliminary drop due to splitting up of "free" morphin present, then a period during which the morphin content is fairly constant, followed by a secondary drop due to the splitting up of the "combined" morphin. This secondary decomposition is greatly retarded by embalming, although there seems to be no effect on the preliminary disappearance of morphin. Marcelet⁸ showed the following order of localization in the human body: liver, stomach, kidneys, heart, brain, and lungs. Morgulis and Levine⁹ conclude that morphin is invariably found in appreciable quantities in the urine and kidney, alimentary tract, liver, lungs, and brain.

Detection of Morphin in the Body after Long Periods.—

Woodman and Tidy recount a case of the recovery and detection of both morphin and meconic acid in the stomach four months after death, the body having lain exposed in an unfinished house.¹⁰ The experiment given on page 434 shows the detection of morphin ten weeks after the death of the animal poisoned with it. In the experiment with liver, described on page 434, the alkaloid resisted the effects of putrefactive

¹ Micro-Chemistry of Poisons, 2d ed., 1885, 512; Univ. Med. Mag., 1890, ii, 399; Chem. News, 1890, lxii, 65 and 79.

² Arch. f. exper. Path. u. Pharm., 1900, xliv, 217.

³ Ergebnisse der Physiologie, 1905, iv, 283.

⁴ Pharm. Weekblad, 1907, xlv, 1353.

⁵ Biochem. Ztschr., 1913, liv, 161.

⁶ Vrtljschr. f. ger. Med., 1913, 3 F., xlv, 1 sup., 198.

⁷ Jour. Amer. Chem. Soc., 1916, xxxviii, 1873.

⁸ Bull. soc. pharmacol., 1918, xxv, pt. 2, 292.

⁹ Jour. Lab. and Clin. Med., 1920, v, 321.

¹⁰ Forensic Medicine and Toxicology, 1877, p. 340.

tissue for thirty-five days. Ipsen¹ was able to detect morphin after a period of nine months, while Palet² was able to recover this alkaloid from decomposed viscera, using the Dragendorff process, seven months after death. Certainly morphin is not to be counted in with the more stable alkaloids; thus its resistance to decomposing effects is far below that of strychnin.

Failure to Detect.—There are many reported cases of failure to find morphin by analysis of the body, even when made shortly after death by poisoning with this alkaloid.³ In an unknown proportion of these cases, without doubt, the poison would have been revealed by closer chemical work with more efficient chemical methods. But there is every reason to believe that *it is not uncommon* in cases of fatal poisoning by morphin for the alkaloid to disappear beyond the reach of analysis—that is, to become so far attenuated that it does not meet the limit of its analytic recovery from the organs in which it lies. In the first place, it is subject to the result possible to poisons generally—that they may be eliminated from the body too late for the vital powers to recover from the injury they have inflicted. In the next place, morphin is liable to chemical changes and decompositions. The conditions which bring about the decomposition of morphin in the body in one case and not in another are far too complex and elusive to be predicted.

Haines⁴ reports a case of analysis of the stomach made for morphin promptly after the death of a woman who had taken from 10 to 15 grains (0.65–0.98 gm.) of the drug with suicidal intent. She lived about eighteen hours after taking the poison. After repeated and careful tests not the faintest reaction for morphin could be obtained. The same authority refers to a considerable number of cases in late years, of known death from opium, in which the poison was not afterward discovered in the stomach.

CODEIN

This alkaloid is present in opium in the proportion of 0.2 to 0.8 per cent., its quantity averaging, therefore, about one-twenty-fourth of that of the morphin in opium. In chemical constitution it is a morphin derivative—methyilmorphin, $C_{18}H_{22}NO_3$ —the methyl group being substituted for the phenolic hydrogen of the morphin molecule. Its graphic structure⁵ may be, therefore, readily seen by making this substitution in the structural formula of morphin as shown on page 516.

Codein crystallizes from dry ether, carbon disulphid, or benzene in anhydrous prisms melting at 155° C. (311° F.). From water or water containing ether it crystallizes with 1 molecule of water of crystallization in colorless, translucent, rhombic prisms, or as a crystalline powder, odorless and slightly efflorescent in warm air. These latter crystals melt at 152° to 153° C. (305.6° to 307.4° F.). One gram of codein dis-

¹ Vrtljaschr. f. ger. Med., 1913, 3 F., xlv, 1 sup., 198.

² Ann. soc. quim. Argent., 1919, vii, 22; Chem. Abs., 1919, xiii, 3203.

³ Taylor, On Poisons, 3d ed., 1875, pp. 556, 559.

⁴ Hamilton's Legal Medicine, 1894, i, 446.

⁵ See Mannich, Arch. der Pharm., 1916, ccliv, 349.

solves in 120 mls. of water, 2 mls. of alcohol, 0.5 mil. of chloroform, and in 18 mls. of ether at 25° C. (77° F.); also in 1.2 mls. of alcohol at 60° C. (140° F.). It is readily soluble in benzene and amyl alcohol, but difficultly soluble in petroleum ether. A saturated aqueous solution of codein is alkaline to litmus. It dissolves very easily in acids to form neutral salts, from which solutions it is precipitated by sodium or potassium hydroxid, but not by ammonium hydroxid. Aqueous solutions are strongly levorotatory. On heating codein with strong mineral acids it is converted into apomorphin just as is morphin, so that such tests as those of Pellagri and Husemann do not differentiate these two alkaloids.

Codein phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 + 2H_2O$) occurs in fine, white, needle-shaped crystals, or as a crystalline powder, odorless and very efflorescent. One gram of codein phosphate dissolves in 2.3 mls. of water, 325 mls. of alcohol, 4500 mls. of chloroform, and in 1875 mls. of ether at 25° C. (77° F.); also in 0.5 mil. of water at 80° C. (176° F.) and in 125 mls. of boiling alcohol. Its aqueous solution is acid to litmus.

Codein sulphate ($((C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 + 5H_2O)$) occurs in long, glistening, white, needle-shaped crystals or rhombic prisms, or as a crystalline powder; odorless and efflorescent in the air. One gram of this salt dissolves in 30 mls. of water and in 1280 mls. of alcohol at 25° C. (77° F.); also in 6.5 mls. of water at 80° C. (176° F.) and in 440 mls. of alcohol at 60° C. (140° F.); insoluble in chloroform or ether. Its aqueous solution is neutral or not more than faintly acid to litmus.

Symptoms of Poisoning by Codein.—Codein resembles morphin in the general features of its action, although it is much less poisonous. It depresses the brain, and causes an exaltation of the activity of the lower parts of the central nervous system. Its depressant action is not so powerful nor as enduring as that of morphin, however, while the stimulation is more evident and involves not only the cord but also the medulla and lower parts of the brain. As mentioned in the discussion of morphin, this latter alkaloid also stimulates rather than depresses the brain in the feline class, but with codein this is true also for the dog, and, to a less extent, for man. In the latter small quantities of codein produce sleep, but this is not so deep and restful as that which follows the administration of morphin, and the patient is liable to be awakened by slight noises, and is restless and often unrefreshed when he awakens. Somewhat larger quantities, instead of inducing sleep, increase the restlessness and cause a considerable exaggeration in the reflex excitability. The respiration is not so much slowed as after morphin, and, according to Winternitz, the excitability of the center is practically unchanged, while morphin reduces it very considerably. The pupil is slightly contracted during the codein sleep, but dilates when the excitement stage follows. Codein does not seem to produce so great constipation as morphin, and in animals often causes purging and diarrhea (Cushny).

According to Lewin, doses of 0.8 gram of codein produce muscle weakness, disturbances of vision, myosis or mydriasis, vertigo, loss of consciousness, slight delirium, muscular contractions, acceleration of

pulse, dyspnea, and collapse. With doses of 0.1 to 0.2 gram there was slowing of pulse, sensation of heat about the head, pain in the head, roaring in the ears, restlessness, pain in stomach, vomiting, abdominal pain.

Fatal Quantity.—It is a difficult matter to state the lethal dose of codein, as recovery occurred in the 6 reported cases of poisoning with this alkaloid. The average pharmacopeial dose of codein or one of its official salts is given as 0.03 gram ($\frac{1}{2}$ gr.). The probable safe dose of this drug may be put at about 0.133 gram (2 gr.). Doses of 0.3 gram (4.5 gr.) would, most probably, produce very unpleasant if not very dangerous symptoms, although recovery is reported from doses of 0.518 gram (8 gr.) in 2 cases.

Treatment of Codein Poisoning.—This is practically the same as that outlined for morphin poisoning, especial attention being paid to the elimination of the drug.

CASES OF POISONING BY CODEIN

CASE 1.—A man took 4 grains (0.259 gm.) of codein and in a half-hour became much exhilarated in spirits. In four hours he was greatly prostrated, pale, and in a profuse perspiration, with scarcely perceptible pulse and pupils slightly contracted. Vomiting was induced by warm water and gave some relief, after which there was repeated vomiting from the effects of the codein. The second day the patient still suffered from nausea and weakness, but gradually recovered. Afterward he took $\frac{1}{2}$ -grain doses of codein twice daily for diuresis, as directed by physician, with benefit.¹

CASE 2.—A hospital patient in advanced phthisis took a quantity of cough mixture containing about 8 grains (0.518 gm.) of codein, his stomach being empty at the time of taking. In about ten minutes the pulse was 142 and weak, the respiration 30, with sighing. Vomiting was then induced, and whisky given. A few hours later the pulse was 120 and bounding, the pupils were closely contracted, there was a feeling of confusion in the head, and intense itching was present over the arms and trunk. He was kept awake, coffee and ether were administered, and the symptoms gradually abated, with recovery on the second day.²

CASE 3.—A young woman, who had been taking $\frac{1}{2}$ -grain (0.016 gm.) doses of codein on the prescription of a physician, took 8 grains (0.518 gm.) at once. One hour later there were nausea and vomiting. The patient became restless and irritable, making some convulsive movements, and suffering intense irritation of the skin over the body and especially upon the back and the forearms. The respirations numbered 12 a minute, there were thirst and a feeling of fulness in the head, and the pupils were contracted to a pin-point. Under "the usual treatment for opium poisoning" the patient improved, and on the second day recovered.³

Chemical Tests for Codein.—The chemical tests for the identification of codein are fairly distinctive when taken together and with observation of the solubilities, this alkaloid being readily soluble in ether and chloroform. Further, codein is precipitated by excess of alkali hydroxids (but not by ammonia), while morphin is soluble in excess of the alkali hydroxids and is precipitated by ammonia. Codein is further distinguished from morphin by not reducing iodic acid, and by not giving a blue color with neutral ferric chlorid solution, nor a

¹ Myrtle, Brit. Med. Jour., 1874, i, 478.

² Walsh, Ibid., 1889, ii, 718.

³ Spratling, Medical Record, 1893, xliv, 81. For further cases see Ambrosoli, Gazz. med. ital. lomb., 1875, xxxv, 41; Mettenheimer, Memorab. Heilbr., 1891, N. F., xi, 136; Medvei, Internat. klin. Rundschau, 1892, vi, 1457; Boissonnas, Rev. méd. de la Suisse Rom., 1919, xxxix, 581.

Prussian blue with a mixture of ferric chlorid and potassium ferri-cyanid.

Codein gives with cold concentrated sulphuric acid, free from any trace of nitric acid, no coloration, but on warming or on long standing (several days) a blue color develops. On the addition of a drop of ferric chlorid solution to the colorless cold sulphuric acid solution of codein (or touching the solution with the point of a glass rod moistened with a solution of ferric chlorid) a deep blue color appears on slight warming, and changes to red on the further addition of a drop of nitric acid. This same blue color, due to oxidation, is given by treating codein with concentrated sulphuric acid containing potassium arsenate. If water or sodium hydroxid solution be added to this latter blue solution, the color will change to orange yellow. In strong nitric acid codein dissolves to a yellow liquid, which should not show more than a slight reddish-brown color on standing. If the solution of the alkaloid in concentrated sulphuric acid be heated to 150° C. (302° F.) and touched with nitric acid, a blood-red color is produced.

Codein, like morphin, is converted into apomorphin on heating with concentrated mineral acids. In consequence, codein will give the Husemann and Pellagri reactions in the same manner as does morphin. With Fröhde's reagent codein gives a yellowish color, which soon changes to deep green and finally blue. With Marquis' reagent codein does not give the initial purple shown by morphin, but strikes a violet changing to blue. With Mecke's reagent¹ (sulphuric acid containing 0.005 gram of selenious acid per mil.) codein produces a green color, changing rapidly to blue, then slowly back to grass green; while with this reagent morphin gives a blue color, changing to green and then to brown. The same play of colors is noted when these alkaloids are treated with Lafon's reagent (1 gm. of ammonium selenite in 20 c.c. of concentrated sulphuric acid). Codein, like morphin, gives the purplish-red color when treated with sulphuric acid and cane-sugar (furfurol test).

Tunmann² has advanced the following microchemical method for differentiating morphin and codein. A little of the suspected residue is sublimed by heating on an asbestos plate, covering the sublimate with a cover-glass, and introducing at the edge of this a drop of hydriodic acid. A slight granular precipitate is thus formed, and this disappears on heating. When the preparation is cooled, crystals of the tetraiodid are immediately formed in the case of morphin, whereas with codein crystals of the tri-iodid appear only after three to five minutes, but more rapidly in the presence of a small drop of alcohol. The morphin tetraiodid crystals are always very flat, quadrangular, mostly rectangular plates, 30 to 50 μ broad by 80 to 120 μ long, and are prismatic and show direct extinction and a blood-red to brownish-red color. The bulk of the crystals are united to ladder- and step-like

¹ Ztschr. f. offent. Chem., 1899, v, 350; see also Morgulis and Levine, Jour. Lab. and Clin. Med., 1920, v, 321.

² Apoth. Ztg., 1916, xxxi, 148; Jour. Chem. Soc., 1916, ex, pt. 11, 655.

aggregates 1 mm. or more long, and these, in turn, are combined to stars and crosses. Pleochroism is either slight or non-existent. Codein tri-iodid crystals are paler, thicker, and smaller, the aggregates being not more than one-third the size of morphin tetraiodid crystals. Single crystals ($20\text{--}50\mu$ by $40\text{--}80\mu$) are rare and form half-moon-like triangles with a concave base and a blunted apex. The majority are twin crystals, which always grow out on the convex side and give butterfly—and goblet-like forms—by which these crystals are recognizable at the first glance. Strong pleochroism exists in this case.

Separation of Codein From Tissues.—Codein is found, both after administration by mouth and by injection, in the stomach, intestines, blood, liver, and other organs. It is excreted mainly in the urine and feces, Bouma¹ finding about 80 per cent. of unchanged codein in these excretions. Prolonged administration apparently fails to induce tolerance or to promote the destruction of codein in the system. The separation of codein from the contents of the stomach, vomited matter, tissues, urine, etc., may be effected by any one of the processes given in the section on General Principles of Toxicology. If codein alone is looked for, the Stas-Otto process is advantageously used; but if other alkaloids are also sought, the modified Dragendorff process is preferable. It is to be remembered, in this connection, that codein is extractable from alkaline solution by ether, amyl alcohol, chloroform, and benzol. From acid solutions amyl alcohol may extract appreciable amounts.

HEROIN

Heroin is a synthetic derivative of morphin prepared by the acetylation of morphin, the hydrogen atoms of the alcohol and phenol groups of this latter alkaloid being replaced by the acetic radical. The formula is, therefore, $\text{C}_{17}\text{H}_{19}(\text{OC}_2\text{H}_5\text{O})_2\text{NO}$, the graphic structure being readily seen by replacing the hydrogen atoms mentioned above by the acetyl group, in the structural formula of morphin given on page 516. It is, hence, diacetylmorphin. This artificial alkaloid forms white prisms or a white crystalline powder, having no perceptible odor, with a bitter taste, and showing an alkaline reaction to litmus. It melts between 171.5° and 173.5° C. (340.7° to 344.3° F.). One gram of heroin dissolves in about 1700 mls. of water, 31 mls. of alcohol, 1.4 mls. of chloroform, and in 100 mls. of ether at 25° C. (77° F.). Readily soluble in benzene. It is saponified by water to α -monoacetylmorphin and by potassium hydroxid to morphin and acetic acid. This deacetylation of heroin takes place to a great extent in the system, so that in cases of poisoning with this drug it has been the usual thing to find residues showing the reactions for morphin itself. Heroin is precipitated by alkalis, but is soluble in excess of these agents.

Diacetylmorphin hydrochlorid ($\text{C}_{21}\text{H}_{23}\text{NO}_5\text{HCl} + \text{H}_2\text{O}$) occurs as a white crystalline powder without odor. Its aqueous solution is neutral or only faintly acid to litmus. It melts at about 230° C. (446° F.) with decomposition. One gram of this salt dissolves in 2 mls. of water at

¹ Arch. f. exp. Path. u. Pharm., 1903, I, 353.

25° C. 77° F.); soluble in alcohol; insoluble in chloroform or ether at 25° C. (77° F.).

Symptoms of Poisoning With Heroin.—Pharmacologically heroin has been rather exhaustively studied and the therapeutic value has been definitely determined.¹ It appears to resemble morphin in its general effects, but acts more strongly on the respiration and less on the cerebral functions. Thus, the respiration is rendered slower with less mental depression than would accompany an equal change elicited by morphin. The slowness in the breathing is, apparently, compensated for by its greater depth, so that the actual diminution of the air inspired is not proportional to the decrease in the number of the movements. This has been disputed and is certainly not invariably true, particularly in man (Cushny). Habitues employ this drug, to a large extent, in the form of snuff.

The literature reveals the following as the more common symptoms of poisoning with heroin: Headache, disturbances of vision, myosis, slow, small, regular pulse (although it may at times be rapid), restlessness, cramps in the extremities, slight cyanosis, respiration slow and deep. Death occurs from respiratory paralysis.

Fatal Quantity.—The pharmacopeial dose of diacetylmorphin or its hydrochlorid is 0.003 gram ($\frac{1}{20}$ gr.). However, for therapeutic purposes this is very frequently increased to $\frac{1}{12}$ or even $\frac{1}{6}$ grain. This latter dose must be regarded as very near a toxic dose. Trawick has reported a case of poisoning with $\frac{1}{12}$ grain of heroin, while other cases of dosages of 0.01, 0.05, and 0.167 gram have been reported with recovery. Death has occurred following doses of 0.6 gram, while in the cases reported by McNally actual recovery of 0.3022 and 0.0436 gram of alkaloid obtained. Dreser² found the lethal dose for rabbits to be one hundred times the therapeutic dose, that of codein ten times the therapeutic dose, while Harnack states that heroin is more toxic to man than to animals.

Treatment of Heroin Poisoning.—As heroin is so readily split up after absorption into morphin, the treatment of these cases resolves itself into that for morphin poisoning, especial attention being directed to control of respiratory symptoms.

CASES OF HEROIN POISONING

CASE 1.—A woman took 0.167 gram of heroin,* after which the following symptoms were noted: Myosis, disturbance of vision, slowing of pulse, subnormal temperature, cramps in the extremities, and collapse.³

CASE 2.—A woman, age thirty-four, took 0.05 gram of heroin hydrochlorid. After twenty minutes she complained of a severe headache and cramps extending to the lower extremities. The pulse was 100 to 110 and regular. The eyes were wide open, with a fixed staring gaze, and reacted to light. She was restless for two hours and talked irrationally.⁴

¹ See Dott and Stockman, *Proceed. Royal Soc., Edinb.*, 1890, 321; Dreser, *Pflüger's Arch.*, 1898, lxxii, 485; Harnack, *Münch. med. Wehnschr.*, 1899, xlv, 881 and 1019.

² *Münch. med. Wehnschr.*, 1899, xlv, 990.

³ Soles, *Therap. Monatsh.*, 1899, xiii, 571.

⁴ *Glasgow, Deutsch. Aerzte Ztg.*, 1908, p. 100.

CASE 3.—An unmarried woman, twenty-nine years of age, underwent an appendectomy and suspension of the uterus. She took the anesthetic nicely and left the table at 10 A. M. At 12.30 $\frac{1}{2}$ grain of heroin was given her for pain. Soon after the breathing became unusual, namely, a deep, stertorous, irregular, jerky respiration with sighing and noisy expiration. Pulse about 42. In a few minutes the respiratory count was 6 per minute and gradually became more shallow. Patient became pulseless and stopped breathing for a perceptible interval. Pupils contracted. Under vigorous treatment with normal saline, atropin, and strychnin with nitroglycerin, patient recovered.¹

CASE 4.—W. K., age twenty, a salesman, was admitted to hospital in an unconscious condition and died seven hours later. The physical examination was comparatively negative save for coolness of the body, a blue mottling of the abdomen, and a weak and irregular heart. The pupils were contracted. The pulmotor was used for intervals of three-quarters and a half-hour respectively. The stomach was washed out with permanganate solution. Respirations were very slow, being 13 per minute on admission to hospital, and after the first use of the pulmotor were 42. They fell down to 16 when the pulmotor was used a second time. Just before death they were 19 per minute. Postmortem examination showed the following: Pupils of the eyes were equal and dilated. External surface of brain presented no change. Upon sectioning the pons, medulla, and cerebellar hemispheres no gross alterations or evidence of disease were noted. An engorgement of the abdominal veins and marked passive hyperemia and edema of the lungs obtained; petechial hemorrhages in the epicardium and in the lining of the greater antrum of the stomach; dilatation of the mitral ring; persistent lymphoid tissue in the thymic body; hyperplasia of the lymph-nodes of the spleen, of the lymph-glands, of the solitary follicles of the stomach, small and large bowel, and of Peyer's patches; hyperplasia of the aorta; slight chronic catarrhal prostatitis; left obliterative fibrous pleuritis; urine contained albumin and sugar in considerable quantities. In the toxicologic examination of the viscera in this case, 0.3022 gram of alkaloid were recovered. The portion extracted from the liver, kidney, spleen, the preservative in which the organs were held, the intestines and intestinal contents gave all the reactions for morphin. The alkaloid extracted from the stomach and stomach contents responded to the tests for heroin.²

CASE 5.—L. D., age thirty-two, entered hospital, from whose records the following transcript is taken: Patient in a comatose condition, respiration slow and grouped over periods of one and one-half minutes, with intervening periods of dyspnea lasting over one minute. Body of patient cold. Skin is dry and lobes of ears are cyanotic. Pulse is slow, small, regular, and soft. Pupils are pin-point, conjunctivæ injected. No paralysis. Lips, mouth, and throat are negative. Heart normal, abdomen lax, no dulness. Extremities flaccid, reflexes present. Postmortem showed the following: Passive hyperemia of the lungs, of the brain, and of the retro-esophageal tissues; marked edema of the lungs, jejunum, and ileum; marginal emphysema of the lungs; slight hyperplasia of the spleen. The lungs did not collapse when the pleural cavities, containing a large amount of fluid, were opened. The pulmonary artery and its branches were empty. The heart was loose and flabby. The inner surface of the calvarium was of a bluish-gray color. A large amount of cerebrospinal fluid was present, being very abundant in the sulci of the vertex of the brain where the convolutions are widely separated. There were no alterations in the fourth ventricle. On the surfaces made by sectioning the brain in the usual way, there was no gross disease. The blood from the heart gave a strongly positive Wassermann reaction. In this case, 0.0436 gram of alkaloid were recovered from the stomach and its contents and a portion of the intestines, unchanged heroin being found in the stomach and contents.³

CASE 6.—G. S., age fifty-nine, retired warehouseman, suffering with diarrhea as a probable result of ptomain poisoning, was given 1.2 grams of potassium bromid without effect. One hour later this was followed by a cachet supposed to contain veronal 0.48 gram and aspirin 0.3 gram. Subsequent analysis of the remaining cachets showed them to contain 0.418 gram (6.97 gr.) of heroin hydrochlorid, which had been dispensed by mistake. In less than one hour the patient was sleeping, face twitching, and skin acting freely. At 5 P. M. he was sleeping soundly but both arms and legs were frequently jerked with strong clonic muscular spasms. By 9.30 P. M. condition was markedly changed. Respiration became labored, ster-

¹ Trawick, Kentucky Med. Jour., 1911, ix, 187.

² McNally, Jour. Lab. and Clin. Med., 1917, ii, 570.

³ Ibid., 1917, ii, 571.

torous, and very slow (7 per minute); face was pallid, dusky, and the spasms of limbs persisted. Pupils were contracted to pin-points and patient could not be roused, though corneal reflex persisted. Muscles of back of neck rigid and, on lumbar puncture, clear fluid not under increased pressure escaped. Condition continued unchanged all night and at 6 A. M. the temperature was 38.3° C., pulse-rate 100, and respirations 14. Patchy bronchopneumonia developed at both bases, and patient died seventy hours after drug was taken. Portions of organs, when subjected to analysis for alkaloids, showed the presence of $\frac{1}{84}$ grain of morphin only.¹

Chemical Tests for Heroin.—Like codein, heroin does not reduce iodic acid, nor does it give a blue color with neutral ferric chlorid, or Prussian blue with ferric chlorid and potassium ferricyanid, although on long standing this latter reaction may appear.

Owing to the ready hydrolysis of heroin, all the reactions given under morphin in which strong acids are used will be shown by heroin in much the same manner as morphin itself. Thus the colors obtained with the Husemann and the Pellagri tests are practically identical, while with Fröhde's reagent heroin shows a purple, which may gradually change to blue; with the Marquis test, the reddish tones may be more prominent with heroin than with morphin. With Denigés' test, heroin gives practically identical results with morphin.

Heroin dissolves in concentrated sulphuric acid without any color other than a slight yellow. With concentrated nitric acid, heroin shows a yellow color, which changes in a few minutes of itself (or at once on heating) to a greenish blue gradually fading to a yellow.

If about 0.1 gram of heroin be heated with 1 mil. of alcohol and 1 mil. of sulphuric acid, the odor of ethyl acetate is recognizable. Morphin and codein do not give this reaction. On adding a little heroin to 2 c.c. of a 10 per cent. solution of urotropin in concentrated sulphuric acid, there appears an immediate golden yellow color changing to saffron yellow and finally deep blue. Morphin gives a purple color with this reaction.² On heating heroin with sulphuric acid and then adding a little chloral hydrate, a brownish-red color appears. Morphin gives a violet color and codein a bluish green, which gradually changes to red. This latter change of color may be made more rapid by adding water or a solution of sodium hydroxid.³ If a solution of platinic chlorid be added to a solution of heroin in 0.5 per cent. hydrochloric acid, the double platinum salt is formed, which is at first amorphous, but later assumes a crystalline form, appearing in burr-like aggregates. These crystals melt at 223° C. (433.4° F.) with decomposition. These crystals readily form in solutions of a strength of 1 : 100. Morphin, under the same conditions, gives an amorphous precipitate of the double platinum salt.⁴

¹ Boyd, *Med. Jour. Australia*, 1919, i, 91. For other cases see Weinzieher, *Wratsch. Jg.*, 1900, xx, 748; Comar and Buvat, *Presse méd.*, 1904, i, 428; *Münch. med. Wehnschr.*, 1904, li, 2312; Gadamer, *Lehrbuch der Chemischen Toxicol.*, 1909, 560; Tolone, *Gazz. internat. di med.*, 1908, xi, 222 and 233; Gordon, *Jour. Amer. Med. Assoc.*, 1921, lxxvi, 927.

² Taylor, *Allen's Commercial Organic Analysis*, 1912, vi, 389.

³ *Ibid.*, 369; see also Richards, *Analyst*, 1919, xlii, 192.

⁴ Danckwortt, *Arch. d. Pharm.*, 1890, ccxxviii, 572; Wright, *Jour. Chem. Soc.*, 1874, xxvii, 1031; Beckett and Wright, *Ibid.*, 1875, xxviii, 312; 1876, xxix, 652.

Separation from Tissues.—Cases 4, 5, and 6 above mentioned indicate that the usual methods for the extraction of heroin from tissues do not show the presence of heroin, owing to the hydrolysis of this alkaloid to morphin. The experiments of McNally indicate that the diacetylation of heroin does not take place in the stomach and is in accord with his finding of heroin in the stomach and its contents, while morphin was shown in the other tissues examined. The method advanced by McNally¹ for the separation of heroin from the tissues is as follows: Extract the alkaloid from the suspected tissue by successive portions of 50 per cent. alcohol acidified with a few drops of 10 per cent. tartaric acid. Keep the temperature of the samples close to 50° C. (122° F.). Allow the combined extractions to remain in a cool place until the fat separates. The fat is separated in a separatory funnel, washed with acidified water, and the washings added to the main extracts. If the sample is allowed to stand overnight, considerable extraneous material settles to the bottom of the flask and can be removed by filtration, washing the residue with 50 per cent. alcohol. Evaporate the alcoholic extracts under diminished pressure, the water-bath being kept well under the boiling-point. The pasty residue is taken up with a little cold acidified water, and the extraneous matter filtered off. The filtrate is allowed to filter into 95 per cent. alcohol, the protein substances and other impurities thus becoming granular on standing and capable of easy filtration. The alcohol is evaporated off under diminished pressure, until the liquid in the distilling flask amounts to about 20 mls. This residue is taken up with cold water, acidified with tartaric acid, and filtered. To the filtrate is added 1 gram of "alcresta" (Lloyd's reagent, see page 431), and the mixture well stirred. The alcresta together with its adhering substances is filtered off and the liquid tested for alkaloid. If any alkaloid remains in the filtrate, more alcresta is added and the mixture filtered. Transfer the alcresta containing the alkaloid to a glass separatory funnel and extract with successive portions of ammoniated chloroform. The chloroform is evaporated, leaving the free alkaloid as a residue. If any fat accompanies the alkaloid, dissolve the residue in a 0.5 per cent. hydrochloric acid solution, filter and re-extract with ammoniated chloroform. The alkaloid is weighed and submitted to the tests outlined above for heroin. The purity of the residue may be shown by volumetric methods,² the melting-point and crystalline appearance of the platinum salt. In most of McNally's extractions a brown resinous product was obtained, in only one instance a crystalline residue appearing.

NICOTIN AND TOBACCO

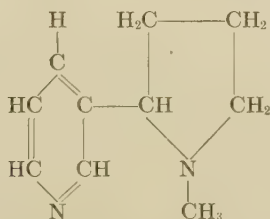
Nicotin is the only constituent of tobacco (*Nicotiana tabacum*) which possesses any toxicologic interest, although at least three other alkaloids (nicotinin, nicotine, and nicotellin) have been isolated from

¹ Jour. Lab. and Clin. Med., 1917, ii, 649.

² See Elvove, Hyg. Lab. Bull., 1909, No. 54; Miller, Amer. Jour. Pharm., 1915, lxxxvii, 248.

tobacco by Pictet and Rotschy.¹ In comparison with the quantity of nicotin found in tobacco, these latter alkaloids exist in very small amount. They are very similar in structure to nicotin, all four alkaloids having 10 atoms of carbon, 2 atoms of nitrogen, and differing in the number of hydrogen atoms.

Nicotin exists in all parts of the tobacco plant, but especially in the leaves, which contain from 0.6 to 8 per cent.² in combination with malic and citric acids. Pipe tobacco contains less nicotin than does that used for cigars, the finer grades of tobacco showing a less nicotin content than the ordinary grades. Nicotin is a rather strong di-acid, ditertiary base, forming salts with one or two equivalents of acid. Chemically speaking, nicotin has the formula, $C_{10}H_{14}N_2$, and is a derivative of pyridin and pyrrolidin with the chemical name, β -pyridyl- α -n-methylpyrrolidin, its structural formula being represented as follows³:



Pure nicotin is a colorless, oily fluid with little odor. On standing, or on dissolving in water, it assumes the peculiar smell of tobacco. It has a sharp, burning taste. On exposure it gradually darkens in color, becoming deep brown, and is eventually changed to a resinous mass. It boils, without decomposition, at 246.1°C . (474.98°F .) under 730.5 mm. pressure, or at 246.7°C . (476.06°F .) under a pressure of 745 mm. It does not solidify at -30°C . (-22°F .). Its specific gravity is 1.0092 at 20°C . (68°F .). It is strongly levorotatory, its specific rotatory power, according to Jephcott,⁴ being -168.40 to -168.66 at 20°C . (68°F .). Its salts are dextrorotatory. Its refractive index is 1.53 at 20°C . (68°F .), that of the commercial nicotin used as an insecticide (95 per cent.) being 1.525, according to Fryer and Fryer.⁵ It is capable of distillation, without decomposition, with steam or in a vacuum. It is soluble in water, alcohol, amyl alcohol, ether, petroleum ether, benzene, chloroform, and oils. Hudson⁶ states that 5 per cent. of nicotin is soluble at any temperature in water and 15 per cent. of water in nicotin, the solubility curve showing the formation of a definite hydrate which separates out from the excess of either water or nicotin between the temperatures of 60° and 210°C . (140° and 410°F .). The

¹ Ber. d. d. chem. Gesellsch., 1901, xxxiv, 696.

² Schmidt, Abderhalden's Biochemisches Handlex., 1911, v, 35.

³ See Pinner, Ber. d. d. chem. Gesellsch., 1893, xxvi, 294; Pictet and Rotschy, Ibid., 1904, xxxvii, 1225; Ibid., 1905, xxxviii, 1951.

⁴ Jour. Chem. Soc., 1919, cxv, 104.

⁵ Analyst, 1919, xlv, 363

⁶ Ztschr. f. physik. Chem., 1904, xlvii, 113.

aqueous solution of nicotin is strongly alkaline in reaction. In the absence of other basic substances, it may be easily determined by titration with standard acid, using methyl red,¹ methyl orange, cochineal, iodeosin, etc., as indicators, 1 c.c. of N/50 sulphuric acid being equal to 0.003246 gram of nicotin. In this connection it is to be stated that, in the examination of insecticides, and even to some extent in the routine toxicologic examinations, pyridin and ammonia may be present and must be eliminated before exact results may be obtained by this method. The monacid salts of nicotin are stable and neutral to litmus and methyl orange, but the diacid salts have an acid reaction. Most of the salts of nicotin crystallize with difficulty, the acid tartrate being an exception. If ether be added to an alcoholic solution of the acid tartrate of nicotin, handsome tufts of small prisms will form, melting at 88° to 89° C. (190.4° to 192.2° F.).

Tobacco is used very widely in the form of pipe tobacco, cigars, cigarettes, and chewing tobacco. To a less extent it is employed as a snuff, which is made from the so-called "snuff leaf" and from refuse tobacco, such as stems and sweepings. Commercially, nicotin finds rather extensive use as a germicide and insecticide. The strength of such solutions varies in nicotin content, the strong commercial nicotin running about 95 per cent., while many of the insecticides show a nicotin value of as low as 35 per cent. or even, in some of the cases reported, of much lower values. Adulteration of this commercial nicotin with ammonia and pyridin has been practised, so that this must be taken into account in the determination of the nicotin content of an insecticide, which comes into question in toxicologic investigations. If ammonia be present it may be recognized by its odor, and may be excluded by converting the basic residue into the oxalate by treatment with oxalic acid and then dissolving the oxalate in absolute alcohol. Under such treatment the oxalate of nicotin dissolves in the alcohol, while the oxalate of ammonium remains undissolved. If pyridin be present it may be separated from nicotin by submitting the residue to distillation in acetic acid solution, under which conditions the pyridin passes over in the distillate, the nicotin remaining behind in the flask. As pyridin has been shown to react with the silicotungstic reagent, which is the best one for the determination of nicotin, the importance of removal of this interfering substance is evident.

There has been much controversy over the question of the presence of nicotin in tobacco smoke. It is undoubtedly true that tobacco smoke varies in character according to the proportion of air admitted during combustion, the oxidation being more perfect in the case of cigarettes, somewhat less with cigars, and least in the case of pipe smoking; in the latter case, a portion of the condensable products being deposited in the liquid state in the stem of the pipe. In the smoke there have been found varying amounts of carbon dioxid, carbon monoxid, hydrogen sulphid, hydrocyanic acid, and pyridin, which have

¹Schick and Hates, *Ztschr. f. Untersuch. d. Nahrungs und Genussmittel*, 1914, xxviii, 269.

little meaning from the toxicologic point of view. Although some workers have asserted the absence of nicotin in the tobacco smoke, yet Melsens, with the confirmation of Kissling, seems to prove that as much as one-seventh of the original nicotin of the tobacco may be found in the smoke, while Lehmann, as well as Garner, show that somewhat more than one-third of the nicotin may be recovered from the smoke. Storm van Leuwen has investigated the actual nicotin content of cigar smoke collected under conditions comparable to those that prevail in the actual performance of smoking. He shows that the common distinction between so-called "mild" and "strong" cigars is no index of the nicotin that may pass into the smoke; nor could the color or even the nicotin content of the leaf be depended on to foretell the outcome of the actual smoke test. That the products of the combustion are absorbed and produce untoward effects is well known from the experience of every smoker. The first cigar almost invariably produces marked toxic effects and will continue to produce them until tolerance is established. The relatively greater effects of inhalation of the smoke, as is usual in cigarette smoking, are due to the greater and more active absorption of the decomposition products from the lungs.¹ Tedeschi² has called attention to the tendency of excessive tobacco smoking to produce seizures resembling epilepsy.

Statements have found currency that numerous brands of cigarettes contain opium, introduced in manufacture. In order to obtain direct proof as to the truth of this allegation, Prescott, Chandler, Long, Haines, and other chemists, made quite an extensive and minute chemical examination of certain leading American brands of cigarettes as to the presence of morphin. Analyses were also made for other alkaloids and for meconic acid. No indication of the presence of morphin was found in any instance, nor was any other constituent of opium found, nor any foreign narcotic whatever in any instance. Testimony to this effect was given by Prescott before a committee of the Legislature of the State of Illinois, at Springfield, on March 28, 1893.

Symptoms and Effects of Poisoning With Nicotin.—Poisonous doses of nicotin administered to man produce a hot, burning sensation in the mouth, which spreads down the esophagus to the stomach, and is followed by salivation, nausea, vomiting, and occasionally purging. There is considerable vertigo, mental confusion, great muscular weakness, and restlessness. Clonic convulsions appear later accompanied by fibrillary twitching of various muscles, and eventually

¹ See Kissling, *Ding. Polyt. Jour.*, 1882, cexliv, 64; Lehmann, *Munch. med. Wehnschr.*, 1908, iv, 723; Garner, *Bull. 141, U. S. Dept. Agric., Bureau of Plant Ind.*, 1909; Bush, *New York Med. Jour.*, 1914, xcix, 519; Storm van Leuwen, *Arch. f. exper. Path. u. Pharmacol.*, 1918, lxxiv, 282; Editorial, *Jour. Amer. Med. Assoc.*, 1919, lxxiii, 108; Asherson, *Chem. News*, 1919, cxx, 150; Hirschfelder, Lange, and Feaman, *Science*, 1920, li, 21; Hahn and Langer, *Ztschr. f. Hyg. u. Infektionskr.*, 1920, xc, 22. For a discussion of the subject of tolerance to nicotin see Edmunds, *Jour. Pharm. and Exper. Therap.*, 1909, i, 1; Dixon, *Proc. Royal Soc. of Med.*, 1911, v, 1; Dixon and Lee, *Quart. Jour. Exper. Physiol.*, 1912, v, 373; Edmunds and Smith, *Jour. Lab. and Clin. Med.*, 1916, i, 315; Armstrong and Evans, *Brit. Med. Jour.*, 1922, i, 992.

² *Riforma Med.*, 1917, xxxiii, 169.

tetanic spasms may appear.¹ In some cases the convulsions are followed by complete relaxation of all parts of the body and the reflexes disappear. The respiration is quick, deep, and labored; while the pulse is generally slow at first and then becomes very rapid.² After very large doses, the pulse may first be accelerated and then slow and feeble. The pupils of the eyes are variably affected in different cases, but most often are dilated, especially in the later stages. The face is pale and the extremities cold. Death is due to respiratory paralysis, the heart continuing to beat after the respiration ceases. After very large doses death may be sudden, the symptoms being those of sudden paralysis of the central nervous system with no convulsions.

Period When Fatal.—The symptoms of nicotin poisoning begin as soon as a poisonous dose reaches the circulation. Very large doses may prove fatal within a few seconds. The course of the poisoning in fatal cases is a very rapid one, measured by minutes rather than by hours. It may cause death without any subjective symptoms, in one reported case of suicide the subject falling dead with the vial from which he had taken the poison still in his hand.³ In the celebrated Bocarmé case, death occurred in five minutes.⁴ In the reported cases of death from tobacco, the period of death is somewhat slower in appearing than with pure nicotin. Sonnenschein⁵ reports the cases of 2 suicides who died in three and five minutes respectively after swallowing 1 or 2 ounces of tobacco. Merriam⁶ mentions the death of a child following the use of a strong decoction of tobacco as a lotion for ring-worm of the scalp. Grahl⁷ describes a case of death following the administration of a decoction of 1 ounce of tobacco in three-quarters of an hour. The poet Santeul is reported to have died two days after drinking wine in which Spanish snuff had been placed by mistake.⁸ Death within five minutes after taking an insecticide containing nicotin, in mistake for whisky, has been reported by McNally, while Feil gives an account of a woman dying twenty minutes after taking such an insecticide by mistake (see cases mentioned below).

Fatal Quantity.—According to Kobert⁹ it may be deduced from records and experiments that 1 grain (0.06 gm.) of nicotin is about the smallest fatal dose for an adult. In the reported cases large doses have been taken, so that it is a difficult matter to state just how much is necessary to produce death. It is highly probable that 3 or 4 drops of the pure alkaloid would cause death, although recovery may follow such or higher doses in those who have become very tolerant to the

¹ See Okushima, *Acta Schol. Med. Univ. Imp. Kioto*, 1919, iii, 151; *Chem. Abs.*, 1921, xv, 271.

² See Ni, *Jour. Lab. and Clin. Med.*, 1920, v, 534; Clerc and Pezzi, *Jour. physiol. et de path. gén.*, 1920, xviii, 965.

³ Harben case, *Pharm. Jour. and Trans.*, 1859–60, n. s., i, 195.

⁴ Procès du comte et de la comtesse de Bocarmé devant la cour d'assises de Hainault, Mons., 1851; Stas, *Bull. acad. de méd. de Belg.*, 1851–52, xi, 202.

⁵ Cited by Weidanz, *Heilkunde*, 1907, 333.

⁶ *London Med. Gaz.*, 1839–40, i, 561.

⁷ *Jour. de Prak. Heilkde.*, 1830, lxxi, 4 St., 100.

⁸ Fontenelle, *Jour. de chim. méd.*, 1836, 2 s., ii, 652.

⁹ *Intoxicationen*, 1906, ii, 1064.

effects of tobacco. Pereiro¹ cites a case in which death resulted from the use of an infusion of 30 grains (2 gm.) of dry tobacco as an enema. As no notation of the percentage of nicotin in this tobacco was given, it cannot be stated what the lethal dose was in this case. In the cases cited by McNally, two individuals drank about 30 c.c. of an insecticide containing 39.84 per cent. of nicotin and died within five minutes (see below). Kobert states that a case is known in which 12 grains (0.8 gm.) of tobacco taken internally caused death.

Treatment.—The treatment of cases of poisoning with nicotin or tobacco consists in the evacuation and washing out of the stomach, and the administration meantime of finely pulverized charcoal partially to absorb the alkaloid. Lorenz² recommends the addition of iodine and tannic acid to the lavage water, and advises the trial of dilute hydrogen peroxid. The poisonous effects are to be met by stimulants, friction rubs, and warmth, promotion of the respiration, and the inhalation of oxygen.

Statistics.—As far as we have been able to find the literature contains record of 29 cases of nicotin poisoning as such. There are many recorded cases of death from tobacco, which has been used as an infusion or decoction for external application or as an enema. The use of tobacco as a snuff or in the form of chewing tobacco has, likewise, resulted in death. So also the accidental introduction of tobacco into food has caused several deaths. Several cases have been cited of the use of tobacco or of nicotin with homicidal intent.

CASES OF POISONING BY NICOTIN AND BY TOBACCO

CASE 1.—The historic case of the trial of the Count of Bocarmé for the murder of his brother-in-law, Gustav Fougnyes, has given a degree of forensic interest to this poison; and the fact that it was Stas under whose hand the analysis was made, determining nicotin in the case, has given chemical interest to the records. It was established that nicotin, "the essential oil of tobacco," prepared by the defendant was forcibly administered, with the result of death in five minutes. In the examination of the body the tongue was found swollen, its epithelium detached, and the blood not coagulated. Nicotin was found in the mouth, throat, stomach, liver, and spleen.³

CASE 2.—In London, in 1858, a gentleman swallowed a quantity of nicotin from a bottle, and almost immediately fell to the floor. There were no convulsions. With a deep sigh, life became extinct. This death resembled one caused by prussic acid or potassium cyanid. The appearances were those of relaxation of the muscles, bloated features, and fulness and lividity about the neck. The odor of nicotin or tobacco was not perceptible about the body. Two or three days after death it was found that putrefaction had occurred, especially in the course of the veins. There was swelling of the neck, arising from effusion of dark liquid blood. The scalp and membranes of the brain were filled with dark-colored blood. The lungs were engorged and of a dark-purple color. The cavities of the heart were empty with the exception of the left auricle, which contained 2 drams (7.5 c.c.) of dark-colored blood. The stomach contained a chocolate-colored fluid; the mucous membrane was of a dark crimson-red color. There was no odor excepting that of putrefaction. The liver was congested. The blood throughout was liquid and

¹ Elem. Mat. Med., 1872, 619.

² Klin. therap. Wehnschr., 1909, xvi, 1298.

³ Orfila, *Toxicologie*; a full account of the case is given in Wharton and Stillé's *Medical Jurisprudence*, 1884, ii, 603; see also *Procès du comte et de la comtesse de Bocarmé devant la cour d'assises de Hainault, Mons., 1851*; Stas, *Bull. acad. roy. de méd. de Belg.*, 1851–52, xi, 202.

dark. Nicotin was found in small quantity in the stomach, also in the liver and lungs, which, however, had been placed in contact with the stomach.¹

CASE 3.—A man applied to himself a decoction of tobacco for the cure of an eruptive disease. Death took place in three hours, with the usual symptoms of tobacco poisoning.²

CASE 4.—A man suffering from pediculi pubis rubbed his entire body with a decoction which he had made by boiling 3000 grains (200 gm.) of tobacco in 2 liters (4 pints) of water. He was seized with vertigo, nausea, heaviness of the head, disturbance of vision, cold sweats, extreme pallor, trembling and weakness of the limbs, etc. The extremities became very cold and purplish in color, and the moisture on the skin was viscous. The pupils were slightly dilated and retained the power of accommodation; they reacted to light. Nausea and vertigo were constant symptoms. There was difficulty of respiration and of speech. The symptoms gradually subsided after three hours.³

CASE 5.—Rudolph D., an infant five months old, was given milk into which tobacco had been put by mistake. After two feedings with this milk, the patient became cyanotic and collapsed. There was profuse sweating of head. Extremities were cold and clammy. Twitching of muscles of face. Both pupils widely dilated. Pulse weak and irregular. Respiration slow and labored. Treatment with atropin, strychnin, brandy, epinephrin, coffee enemas, etc., with no avail. Death followed. Skin was covered with purple blotches, which varied from size of 10-cent piece to that of a half-dollar.⁴

CASE 6.—A woman, age fifty-two, drank by mistake from a bottle containing an infusion of tobacco, thinking it was caseara. Immediately pain in bowels was complained of. Patient attempted to swallow but could not do so. General convulsions were followed by relaxation and death in about twenty minutes. The insecticide, on examination, showed 12 per cent. of nicotin.⁵

CASE 7.—A man drank an unknown quantity of liquid containing 44.84 per cent. of nicotin. The concentrated solution of the insecticide was kept in a cognac bottle, a small portion of which was diluted in a large volume of water for spraying lettuce and radishes. A similar bottle containing liquor was kept on the shelf alongside the insecticide. The man took one swallow of the liquid, realized immediately his mistake, and ran 75 feet to the house, raised a bottle of milk to his lips, dropping dead before he was able to take a drink of the milk.

CASES 8 and 9.—Two men, celebrating the first report of the armistice, visited the home of a mutual friend, who was asked to give them a drink of liquor. Three bottles of beer were opened; the host then recalled that he had a bottle of whisky in the pantry. This latter bottle was produced and three whisky glasses filled. The capacity of these glasses was 90 c.c., it being stated that they were about two-thirds filled with the fluid from the flask. The two visitors drank about half of the portion given to them, one making the remark "what funny tasting booze." Both men had a sensation of choking, dropped to the floor gasping for air, became cyanotic, dying within five minutes. Neither of the men vomited. One of them had a frothy mucus coming from the mouth and nose and had urinated and defecated. The host claimed he drank some of his liquor and immediately produced emesis by drinking a large quantity of salt and water. A postmortem examination upon these two bodies, made three hours after death, showed an intense hyperemia of all of the organs. The stomach was highly congested in both cases, having the odor of alcohol. Upon opening the thoracic and abdominal cavities, there was no distinct odor of nicotin. The head was not posted. Stomachs were removed for chemical examination. The stomach and contents of E. N. weighed 345 grams. A volatile distillate of 200 grams of stomach and contents showed the presence of 0.4465 gram of nicotin, making a total of 0.7702 gram in the organ. The stomach and contents of F. P. weighed 659 grams. From 115 grams, 0.8673 gram of nicotin was recovered, a total of 4.9609 grams for the organ. Examination of the liquor remaining in the flask from which the poison had been taken showed it to contain 39.84 per cent. of nicotin, the silicotungstic acid method being employed.⁶

¹ Taylor, *Guy's Hosp. Reports*, 1858, 354.

² Nomias, *Amer. Jour. Med. Sci.*, 1865, lxxv, 268.

³ Auché, *Amer. Jour. Pharm.*, 1891, lxiii, 463.

⁴ Reynolds, *Jour. Amer. Med. Assoc.*, 1914, lxii, 1723.

⁵ Feil, *Cleveland Med. Jour.*, 1916, xv, 174.

⁶ McNally, *Jour. Lab. and Clin. Med.*, 1920, v, 213. For other cases of tobacco poisoning see Ansiaux, *Jour. de chim. méd.*, 1827, iii, 23; Eade, *Lancet*, 1849, ii, 480; Skae, *Edinb. Med. Jour.*, 1855, i, 643; Oppolzer, *Wien. med. Presse*, 1866, viii, 1151;

Postmortem Appearances.—The blood is dark and fluid. Congestion of the brain and internal viscera is usually found. Odor of tobacco may be present in the stomach and other organs. If death has not occurred rapidly, the appearances of a more or less intense gastro-enteritis are observed. There is nothing especially characteristic in the findings.

Chemical Tests for Nicotin.—1. For the recognition of nicotin, the following general points are of value: Its fluidity and volatility; its characteristic odor; its boiling-point of 246.7° C. (476.06° F.) at 745 mm. pressure. General alkaloidal reagents will precipitate nicotin from quite dilute solutions, a point of distinction from coniin. Thus, tincture of iodine gives a yellow precipitate which soon becomes purplish or reddish brown; phosphomolybdic and phosphotungstic acids give precipitates even at dilution of 1 : 40,000; gold chlorid produces a yellow or brown amorphous precipitate, especially in neutral solutions of nicotin, which precipitate is readily soluble in excess of nicotin and in caustic alkalis, but insoluble, or nearly so, in acetic and hydrochloric acids, a distinct cloudiness being observed at dilutions of 1 : 10,000; platinum chlorid gives a yellow amorphous precipitate, which soon becomes crystalline, at a dilution of 1 : 5000 of nicotin; mercuric chlorid produces a white, curdy precipitate, which becomes crystalline on standing in dilutions of 1 : 3000, which precipitate is soluble in acetic and hydrochloric acids and also in ammonium chlorid, but from this latter solvent the nicotin separates to some extent on standing for a time; picric acid gives an amorphous precipitate which soon changes into crystalline tufts, the reaction indicating nicotin in a dilution of 1 : 25,000; potassium mercuric iodid, likewise, gives a crystalline precipitate at a dilution of 1 : 25,000. With coniin the concentration of the alkaloid must be considerably greater than those mentioned above before reactions occur. Silicotungstic acid or potassium silicotungstate, when added to a solution of nicotin containing an excess of free hydrochloric acid, yields an immediate precipitate at dilutions of 1 : 300,000, while at a dilution of 1 part of nicotin per million a crystalline precipitate appears on allowing the mixture to stand for twenty-four to forty-eight hours. Coniin, with this reagent, yields precipitates only at dilutions of 1 : 5000 or stronger.¹

2. **Crystallization Test.**—If a few drops of nicotin be placed on a watch-glass and a few drops of concentrated hydrochloric acid on

Shaw, Phila. Med. Times, 1878, viii, 528; Hardman, Atlanta Med. and Surg. Jour., 1884, n. s., i, 648; Posner, Allg. Med. Centr. Ztg., 1894, xviii, 481. For further cases of nicotin poisoning see Witt case, Pharm. Jour. and Trans., 1858-59, xviii, 46; Harben case, Ibid., 1859-60, xix, 195; Fonssagrives and Besnon, Ann. d'hyg., 1861, 2 s., xv, 404; Borsarelli and Bruno, Giorn. d. r. Acad. di med. di Torino, 1867, 3 s., iv, 745; Simons, Nederl. Tijdschr. v. Geneesk., 1877, 2 R., xiii, 233; Boutmy, Ann. d'hyg., 1880, 3 s., iv, 201; Johnson, Lancet, 1890, ii, 337; Erlendsson, Ugesk. f. Laeger, 1911, lxxiii, 368; Deszimirowics, Wien. klin. Wehnschr., 1918, lxxviii, 1311; Suchy, Ibid., 1422; Beneke, Münch. med. Wehnschr., 1919, lxvi, 1463 (3 cases); McNally, Jour. Lab. and Clin. Med., 1920, v, 213 (2 cases not cited above); McNally, Jour. Amer. Med. Assoc., 1921, lxxvii, 377 (recovery after drinking liquid containing 42.4 per cent. nicotin); McNally, Jour. Lab. and Clin. Med., 1922, 8, 83 (7 cases).

¹ See Sanchez, Semana Médica, 1921, xxviii, 217.

another watch-glass, one of these glasses being inverted over the other, a white cloud is produced, which is not so dense as in the case of coniin. In the case of nicotin no crystals will be observed on the glasses, while with coniin a prompt appearance of crystals of coniin hydrochlorid will be noted. If this test be made by evaporating a few drops of concentrated hydrochloric acid with a few drops of nicotin, a varnish-like residue will appear, which is amorphous, but which will change to a distinctly crystalline deposit on allowing it to stand in a desiccator over sulphuric acid for some time. With coniin, the formation of crystals is almost immediate.

3. **Roussin's Test.**—If an ethereal solution of iodine be added to an ethereal solution of nicotin, a brownish-red amorphous precipitate is produced which, after standing for some hours, is converted into a crystalline mass of long, ruby-red needles. This reaction occurs at a dilution of about 1 : 100, while with more dilute solutions the amorphous phase of the reaction may be absent. These crystals are known as "Roussin's crystals," and are not formed with coniin. If the nicotin be resinous these crystals are formed with difficulty.

4. **Melzer's Test.**—If a drop of nicotin or $\frac{1}{2}$ to 1 c.c. of a dilute solution of nicotin be heated to boiling with 2 or 3 c.c. of epichlorhydrin, the mixture becomes distinctly red. Coniin gives no reaction with this reagent.¹

5. **Schindelmeyer's Test.**—If nicotin that is not resinous is treated with a drop of formaldehyd solution (which should not contain any formic acid), and then with a drop of concentrated sulphuric or nitric acid, the mixture assumes an intense rose-red color. If the nicotin and formaldehyd be allowed to stand for several hours, a solid compound is formed which gives a more pronounced color on the addition of nitric acid. If this latter technic is employed the formaldehyd must not be in excess, otherwise the solution becomes green after a time and rapidly decomposes. This test is not given by coniin, trimethylamin, piperidin, pyridin, or anilin, nor by the ptomaines resembling nicotin.²

6. **Tunmann's Test.**—Dissolve a few crystals of para-dimethylaminobenzaldehyd on a watch-glass in a drop of fuming hydrochloric acid, adding thereto from the side a drop of the aqueous solution of nicotin. A rose color develops immediately at the surface of contact, then a violet-red zone results, and finally the entire liquid becomes violet red. The color increases in intensity and persists for ten to twenty-four hours. On like treatment coniin and pyridin give no color. Anilin yields in not too dilute solutions a red color, but immediately precipitates a dyestuff in the form of red needles. By this test nicotin may be detected in cigar smoke readily.³

Biologic Test for Nicotin.—If a very small amount of nicotin

¹ Ztschr. f. anal. Chem., 1908, xxxvii, 357.

² Pharm. Zentral-Halle, 1899, xl, 703.

³ Apoth. Ztg., 1918, xxxiii, 485; Chem. Zentralbl., 1919, ii, 227. For the Vanillin test of Sanchez, see Semand Méd., 1921, xxviii, 61.

($\frac{1}{200}$ to $\frac{1}{100}$ drop, 1 c.c. of a 1 : 1000 solution) be injected into the dorsal lymph-sac of the frog the animal rapidly becomes uneasy, and in five to ten minutes, or even less, assumes a peculiar position as follows: the forelegs are pressed backward against the sides of the body, and the hind legs are drawn up in such a position that the thighs are at right angles to the body, and the legs are fixed so that the feet rest upon the back. If the legs are moved from this position they at once resume it when released. The respiration is at first accelerated and then becomes slow. Slight muscular spasms, especially in the hind legs, may be noted. With larger doses a severe clonic spasm results, followed by fixation of the legs in the position mentioned above, slowing or stoppage of respiration, fibrillary contractions, and general muscular relaxation.

Separation of Nicotin From the Tissues.—This may be done by the usual Stas-Otto process, followed by the determination of the amount of nicotin by titration with standard acid, using methyl red or iodeosin as indicators: 1 c.c. of N/50 sulphuric acid equals 0.0032426 gram of nicotin. This method is subject to both positive and negative errors; the first owing to the possible presence of alkaline substances other than nicotin in the residues obtained; the second on account of the possibility of loss of substance, or incomplete extraction, in the rather extensive manipulations necessary. Dangelmayer¹ has shown that trichlorethylene extracts nicotin quantitatively from alkaline solutions, and that the nicotin may be recovered by shaking this extract with dilute sulphuric acid.

It has been shown by Bertrand and Javillier² that the precipitation of nicotin in the presence of an excess of hydrochloric acid proceeds quantitatively when silicotungstic acid or potassium silicotungstate is added to a hydrochloric acid solution of nicotin. This property enables us to make a quantitative determination of the amount in the tissues, without the same possibilities of error inherent in the other methods. In the process recommended, advantage is taken of the fact that nicotin is volatile with steam from alkaline solutions. A definite amount of the finely divided organ, or a definite volume of the stomach contents or other fluid, is placed in a distilling flask and a sufficient amount of water and sodium hydrate solution added to make the mixture of the consistency of thin gruel and strongly alkaline in reaction. A few pieces of glass or pumice may be placed in the flask to prevent bumping. Distillation is then carried out with a rapid current of steam in the usual manner, the distillate being collected in a large flask containing 15 or 20 c.c. of 10 per cent. hydrochloric acid. Continue the distillation until a portion of the distillate shows no opalescence when treated with a few drops of the 10 per cent. solution

¹ Chem. Ztg., 1918, xlii, 290; Chem. Abs., 1919, xiii, 2958.

² Bull. d. Sc. Pharmacol., 1909, xvi, 7; Bull. Acad. roy. Belg., 1909, 1042; Bull. Soc. Chim., 1909, v, 241; see also Guglielmelli and Hardh., Ann. soc. quin. Argentina, 1910, vii, 121; McNally, Jour. Lab. and Clin. Med., 1920, v, 213; Taigner, Ztschr. f. anal. Chem., 1919, lviii, 346; Heiduschka and Wolf, Schweiz. Apoth. Ztg., 1920, lviii, 213 and 229.

of silicotungstic acid followed by a few drops of hydrochloric acid (if nicotin be present in a dilution of 1-in 300,000, an opalescence will appear almost immediately). After the distillation is complete, make the distillate up to a definite volume and filter through a dry filter, testing a portion of the filtrate with methyl orange or methyl red to be certain that the reaction is still acid. Measure with a buret an aliquot portion of the filtered distillate, allowing it to flow into a beaker or small flask. Add a few cubic centimeters of the 10 per cent. hydrochloric acid (3 or 4 c.c. for each 100 c.c. of liquid taken), and follow this with a few cubic centimeters of 10 per cent. solution of silicotungstic acid (McNally recommends 1 c.c. for every 0.01 gram of nicotin suspected); mix thoroughly and allow to stand for eighteen to twenty-four hours. At the end of this time filter the crystalline precipitate through a quantitative known ash filter, and wash with water containing a little hydrochloric acid. The original filtrate should be tested with a few drops of the nicotin distillate in order to insure an excess of the reagent in the original mixture, and likewise the washing should be continued until all of the excess silicotungstic acid is removed from the precipitate. After the washing is complete, transfer the filter and precipitate to a weighed platinum crucible, dry carefully, and incinerate first over the ordinary Bunsen lamp and then over the blast lamp for a few minutes. Cool in a desiccator to constant weight. If the weight of the incinerated residue be multiplied by 0.114 the product yields the amount of nicotin in the aliquot portion of the distillate taken for the determination, as the composition of the precipitate given by silicotungstic acid with nicotin is $12\text{WO}_3 \cdot \text{SiO}_2 \cdot 2\text{H}_2\text{O} \cdot 2\text{C}_{10}\text{H}_{14}\text{N}_2 \cdot 5\text{H}_2\text{O}$. Proper calculation gives the total nicotin in the complete distillate, and likewise in the total original organ from which the portion was taken for determination.

Nicotin-like Ptomains.—From the decomposed intestines of a man who had been dead six weeks Wolckenhaar¹ obtained by extraction with ether from an alkaline solution, a base that bore some resemblance to nicotin. This substance was fluid and at first yellow in color, but on being exposed to the air it became brownish yellow. It was strongly alkaline in reaction, and gave off an odor resembling nicotin but stronger, not ethereal, benumbing, and similar to that of fresh poppy-heads. It was freely soluble in water, and its aqueous solutions did not become cloudy on the application of heat. The solutions were bitter and pungent to the taste, and their odor did not disappear on saturating the base with oxalic acid. The hydrochlorid was yellow, had a strong odor, and became moist on exposure to the air. Under the microscope this compound showed no crystalline structure. It differed from nicotin in its reactions with potassiobismuthic iodid, gold chlorid, iodine solution, mercuric chlorid, and platinum chlorid. It failed to give the Roussin test.

Rörsch, Fassbender, Schwanert,² Liebermann, and Selmi have

¹ Corr.-Bl. d. Ver. anal. Chem., 1878, i, 33 and 37; Otto, Ausmittel. der Gifte, 6te. Aufl., 1884, 96.

² Ber. d. d. chem. Gesellsch., 1874, vii, 1332.

found nicotin-like substances in decomposing animal tissue when there was no possibility of true nicotin being present.

PHYSOSTIGMIN

This base, also called eserin, is the characteristic poisonous alkaloid of the Calabar bean (*Physostigma venenosum*), also known as the ordeal bean, the esere nut, or the chap nut. The Calabar bean is oblong or ellipsoidal, somewhat compressed reniform, from 15 to 30 mm. in length, and from 10 to 15 mm. in thickness; externally reddish or chocolate brown, smooth, somewhat wrinkled near the brownish-black groove, the latter being about 2 mm. in width and extending almost the entire length of the convex edge, and in which are found frequently the remains of the white membranaceous funiculus, the margins of the seed-coat on both sides of the groove somewhat elevated, of a yellowish-red or brownish-red color and somewhat thickened; embryos large, white, with short hypocotyl and two concavoconvex cotyledons; taste at first starchy, afterward acid. The powder is grayish white, starch grains numerous, from 0.005 to 0.15 mm. in diameter, ellipsoidal or somewhat reniform, and usually with a distinct cleft and frequently with radiating or irregular fissures; fragments of seed-coat with very thick, reddish-brown cells, being either palisade-like or very irregular and resembling stone cells, but the walls are not lignified. The seeds should yield not less than 0.15 per cent. of the alkaloids of physostigma and not more than 3 per cent. of ash. The official preparations of the bean are the extract and the tincture, the former yielding not less than 1.7 per cent. nor more than 2.3 per cent. of the alkaloids of physostigma, while the latter yields not less than 0.013 per cent. nor more than 0.017 per cent. of these alkaloids. The official salt of physostigmin is the salicylate, the sulphate, although used to a considerable extent, no longer being recognized by the Pharmacopœia.

The first chemical examination of Calabar beans was conducted by Jobst and Hesse,¹ who ascertained that the poisonous effects were due to an alkaloid which they designated physostigmin. This substance was obtained by them only as an amorphous, varnish-like mass, but later Vée² succeeded in isolating the alkaloid in a crystalline state and proposed for it the name eserin. Harnack and Witkowski³ indicated the presence of a second alkaloid, for which they proposed the name calabarin, but later researches, especially of Ehrenberg,⁴ have shown that this alkaloid was, in all probability, a product of decomposition and could not have pre-existed in the beans. Still later, Böhringer and Söhne⁵ obtained a crystalline base which they termed "eseridin," and was converted, on heating with mineral acids, into physostigmin. Ehrenberg succeeded in isolating another alkaloid termed "eseramin,"

¹ Ann. der Chemie, 1864, cxxix, 115.

² Jahresber. u. Chem., 1865, 456.

³ Arch. f. exper. Path. u. Pharm., 1876, v, 401.

⁴ Verh. Ges. Deutsch. Naturf. Aerzte, 1893, ii, 102.

⁵ Pharm. Post, 1888, xxi, 663. See also Eber, Pharm. Ztg., 1892, xxxvii, 483.

while Ogui¹ has described a further alkaloid under the name of isophysostigmin. Salway² isolates a new alkaloid which he styles physovenin which is probably an intermediate product in the conversion of physostigmin into eserolin. This latter worker isolated eseramin, but could find no evidence of the presence of isophysostigmin or of eseridin. Polonovski³ describes an oxidation product of eserine, which he styles geneserin.

Physostigmin is a monacid, tertiary base, and contains a CO.NHMe complex, since CO₂ and methylamin are eliminated on heating with aqueous KOH. Its chemical formula is C₁₅H₂₁N₃O₂, its graphic structure being still unsettled. It forms crystals which when pure are colorless, but which often have a pale red tint. It is almost tasteless. If crystallized from benzene, the crystals are large, apparently rhombic, and melt at 105° to 106° C. (221° to 222.8° F.), according to Petit and Polonovsky,⁴ although Salway believes these crystals to be dimorphous as he obtained stout prisms melting at 86° to 87° C. (186.8° to 188.6° F.), which crystallized in the presence of a crystal of the more stable variety, melted at 105° to 106° C. (221° to 222.8° F.). It is very slightly soluble in water, readily soluble in alcohol, ether, chloroform, benzene, and carbon disulphid; but insoluble in petroleum ether. It is levorotatory, the value for the specific rotation in chloroform solution being -75.8° to -82°; and in benzol or toluol, -120°. Its solutions are strongly alkaline to litmus, and precipitate ferric hydroxid from a solution of ferric chlorid. It does not yield any definite aurichlorid or platinochlorid, but does form a well-defined picrate, which crystallizes from dilute alcohol in feathery, yellow needles melting at 114° C. (237.2° F.).

Physostigmin salicylate occurs in colorless or faintly yellowish, shining, acicular, or short columnar crystals; odorless. It acquires a red tint when long exposed to light and air. As it is tasteless, great caution must be used in submitting a residue containing it to the taste test, owing to the possibility of an overdose. One gram of this salt dissolves in 75 mils. of water, 16 mils. of alcohol, 6 mils. of chloroform, and in 250 mils. of ether at 25° C. (77° F.); also in 16 mils. of water at 80° C. (176° F.), and in 5 mils. of boiling alcohol. Its cold, saturated aqueous solution is neutral or at most only faintly acid to litmus. Upon standing twenty-four hours, this solution usually acquires a pink color, which is rapidly produced by the addition of a few drops of sodium hydroxid solution.

Symptoms of Poisoning.—The symptoms of poisoning vary little in different animals; in the dog and rabbit, the first results of a large dose of physostigmin are weakness in the voluntary movements and a curious tremor and muscular twitching, beginning in the hind legs, but soon extending over the whole body. The animal falls on one side and cannot raise itself again, although it makes efforts to do so when

¹ Apoth. Ztg., 1904, xix, 891.

² Jour. Chem. Soc. Trans., 1911, xcix, 2148; Ibid., 1912, ci, 978.

³ Bull. soc. chim., 1917, xxi, 191. See also Max and Polonovski, Ibid., 1918, xxiii, 335 and 356.

⁴ Bull. Soc. chim., 1893 (iii), ix, 1008.

touched. The saliva and tears are increased, the bowel is often evacuated, and, with the dog, vomiting is common. The respiration is at first rapid and deep, and later slow and dyspneic; the heart is weak and slow, and the pupil is contracted to a small point. These symptoms become more marked, as more of the poison reaches the blood, until the respiration ceases. In cats these symptoms of depression and paralysis are preceded by a stage of increased movement and evident anxiety, but the later symptoms resemble those in the dog (Cushny). In man physostigmin elicits practically the same results as in the dog, namely, vomiting and pain in the stomach, dyspnea, giddiness, and muscular weakness, contraction of the pupil, salivation, and perspiration. The heart is slow, muscular twitching may be present, and complete collapse follows. The researches of Harnack and Witkowski,¹ Schweder,² Magnus,³ and Kréss⁴ have shown that physostigmin has a central and peripheral action. The central action is shown in the paralysis of the brain and cord, after stimulation; while the peripheral action is indicated in the stimulation of the striped musculature and the glands leading to oversecretion, excessive mucous secretion, and stimulation of peristalsis. While the pupils are ordinarily contracted by physostigmin, this is by no means a uniform finding as dilatation may be noted as in the cases reported by Leibholz.

Fatal Quantity.—It is a difficult matter to state the probable fatal dose of this alkaloid, as only two reports of death are found in the literature. In one death followed in a very short time after the eating of six of the beans, while the dose in the other case is indefinite, the only information in this case being that an ampule, marked "Physostigminum sulfuricum, Merck, 5 g." was found in the room in which the death occurred. However, quite a few cases of toxic action from the use of the alkaloid in ophthalmology have been reported⁵ from varying dosages, while Leibholz⁶ reports the attempted suicide of two women from a dosage of 0.1 gram of the sulphate. Christison⁷ reports, on the basis of self-experimentation, quite marked toxic effects from taking 6 grains of the seed followed on the next morning by a further dose of 12 grains.

CASES OF POISONING BY PHYSOSTIGMIN

CASE 1.—In 1864, 45 children and 1 adult were poisoned in Liverpool by reason of eating the Calabar beans. The sweepings of a ship, from the west coast of Africa, had been thrown on a heap of rubbish; the children found the beans and ate them. A boy, age six, who ate 6 beans, died in a very short time. The principal symptoms were severe griping pains, constant vomiting, and contracted pupils. In addition to these symptoms, the face was pale, and the eyes were bright and protruding. In attempting to walk, the children staggered about as if they were drunk.⁸

¹ Arch. f. exper. Path. u. Pharm., 1876, v, 401.

² Dissert., Dorpat., 1889.

³ Pflüger's Archiv, 1905, cviii, 1.

⁴ Ibid., 1905, cix, 608.

⁵ See Speer, Therap. Gaz., 1904, xxviii, 443; Gassicourt, Gaz. heb. de Med., 1876, xiii, 109; Dunlop, Lancet, 1887, i, 621.

⁶ Vrtljschr. f. ger. Med., 1892, 3 f., iii, 284.

⁷ Pharm. Jour., 1855, p. 474. See also Fraser, Edinb. Med. Jour., 1864, ix, 36, 123 and 235.

⁸ Cameron and Evans, Med. Times and Gaz., 1864, ii, 406.

CASE 2.—A nine-year-old child, suffering from chorea, was given $\frac{1}{2}$ mg. of eserin subcutaneously. One-fourth hour thereafter, the patient cried out, vomited copiously, and complained of marked headache. Soon after profuse sweating was noted in face and upper part of body. Saliva was increased. Pulse somewhat slower than normal, fine and fluttering. Contraction of pupils. Collapse followed by recovery.¹

CASE 3.—Pauline W., age twenty-four, and Minna M., age eighteen, were suddenly taken sick with symptoms which suggested poisoning. They complained of feeling badly and suddenly became unconscious, and lay motionless for some time with deep-red color of face. In both cases, first in that of Minna M., after some time marked vomiting was observed. On arrival of physician, Minna M. was conscious and lay with very red face complaining of marked pain in stomach and bowels. Pupils were maximally dilated and reacted to light. Pulse was full and of strong tension, 60 per minute. Respiration shallow, rapid, and stertorous. Pauline W. became conscious in about a half hour and showed the same picture. Both vomited frequently. Women admitted they had attempted to commit suicide by taking eserin obtained from the table of their master. Each had taken 1 ampule containing 0.1 gm. of Merck's "physostigmin sulphate."²

CASE 4.—On November 5, 1910 the body of Heinrich von T., a pharmaceutic assistant in Graz, was sent to the morgue. It was found about noon on November 4th in a room of a hotel, in which he boarded, under conditions which pointed to suicide from poisoning. He lay across the bed, the coverings of which were soiled with vomitus and feces. A complete postmortem examination was made (see below), and examination of the organs revealed the presence of physostigmin. Later a bottle marked "Physostigminum sulfuricum, Merck, 5 g." was found in the hotel room. How much of this was taken by the man is unknown.³

Postmortem Appearances.—Slight hyperemia of brain. Lungs strongly distended and edematous. Mucous membrane of tongue and the pharyngeal walls strongly swollen and dusky colored; epithelium desquamated in upper portion of trachea, lower down swollen. Stomach strongly extended, mucous membrane markedly reddened and swollen and covered with a tenacious mucus feeling almost soap-like. Some hemorrhage in stomach. Large intestine markedly narrowed and almost empty, mucous membrane swollen and covered with a tenacious grayish mucus. The chief points of interest in the case of Kratter (cited above), which is the only one reported in which a postmortem was made, are the hyperemia of the brain and its coverings; the evidences of stimulation of mucous membrane of the stomach and duodenum; the hypervelocity of the blood and its accumulation in the lungs, heart, and large vessels; the subpleural ecchymoses; and the marked narrowing of the large intestine.

Chemical Tests.—1. **Rubreserin Test.**—On exposure to air and light, an aqueous solution of eserin becomes red, and ultimately dark brown with formation of a red crystallizable coloring-matter called rubreserin. On treating this reddened solution with a reducing agent, such as hypophosphorous acid, sulphurous acid, hydrogen sulphid, sodium thiosulphate, or nascent hydrogen in the presence of a trace of free acid, the liquid is decolorized. If the colorless aqueous solution be shaken for some time with an excess of potassium or sodium hydroxid, it rapidly acquires a pink-red color. On agitation with chloroform, the rubreserin is dissolved out and colors the chloroform orange red.

¹ Lodderstaedt, Berl. klin. Wehnschr., 1888, xxv, 336.

² Leibholz, Vrtljschr. f. ger. Med., 1892, (III), iii, 284.

³ Kratter, Vrtljschr. f. ger. Med., 1912, 3 f., xliii, II Supp., 262.

Barium hydroxid solution may be substituted for the caustic alkali. This first produces a white precipitate which soon becomes red on being shaken.

2. Ammonia Test.—If a minute quantity of physostigmin or one of its salts be treated with an excess of ammonia and evaporated to dryness on the water-bath, it turns in succession pale red, red, yellowish red, yellow, green, and finally blue, this latter blue residue being known as eserin blue. This dissolves in alcohol with a blue color. Excess of dilute mineral acid or acetic acid, added to this solution, changes the color to red, the solution showing a strong reddish fluorescence. Examined spectroscopically the blue alkaline solution shows one absorption band in the red; while the red acid solution exhibits one absorption band in the yellow. On treating the blue solution with reducing agents, the solution first becomes red and then is decolorized.¹

3. Nitric Acid Test.—If a solution of physostigmin or one of its salts be heated to boiling and a few drops of strong nitric acid be added, an orange-colored liquid is obtained, which on addition of sodium hydroxid in excess yields an intensely violet solution, becoming wine red on dilution with water. This violet color is changed to pale orange by acids and restored by alkalis.² This test has been modified by da Silva³ as follows: A minute fragment of physostigmin or one of its salts is treated in a porcelain dish with a drop or two of fuming nitric acid. The clear yellow solution changes to orange when heated to 100° C. (212° F.), and on evaporation to dryness on the water-bath, while stirring, a green residue is obtained, which has been called chlor-eserin. This dissolves in water, or more readily in strong alcohol with deep green color. Spectroscopic examination shows a band in the red, and a broader but fainter band in the blue and violet, and a very feeble band in the orange.

With strong sulphuric acid, solid physostigmin yields a yellow or brownish coloration, which gradually changes to orange or red. Concentrated hydrochloric acid also produces a pink or reddish color. This reddish-brown color of the acid solutions is noted in the extraction process. Bromin water, if not in excess, also gives an intense red color with physostigmin in solution or in the solid state.

Biologic Test.—If 2 or 3 drops of a very dilute solution of physostigmin or one of its salts be dropped in the eye of a cat, contraction of the pupil will be shown within twenty minutes, as a rule. While all cases of poisoning do not show this contraction of the pupil, yet it rarely, if ever, fails when applied to the eye of an animal.

Separation From the Tissues.—This alkaloid is separated from the tissues by either the Dragendorff or the Kippenberger process. Dragendorff recommends benzene as the immiscible solvent, but Kratter prefers chloroform for the first phase of the shaking-out process, and alcohol-containing chloroform later followed by a chloroform-

¹ See Nagelvoort, Flückiger's Reactions, 1893.

² Saul, Pharm. Jour., 1887 (III), xvii, 642; 1893 (III), xxiv, 300.

³ Compt. Rend. Acad. d. Sci., 1893, cxvii, 330.

ether mixture, the physostigmin being taken out in the second phase. In this process it is noted that the acid extract of the organs has a peculiar reddish-brown color, which becomes clear red on alkalinizing. Physostigmin seems to be, judging from the report of Kratter, fairly well distributed throughout the organs and is separated unchanged in the urine. Further, this alkaloid does not seem to be appreciably affected by processes of putrefaction, as Kratter allowed the organs to putrefy for seven months and was able to detect the alkaloid with ease.

STRYCHNIN AND NUX VOMICA

General Description.—Many of the species of *Strychnos*, a genus of plants of the Order *Loganiaceæ*, contain certain alkaloids, strychnin, and brucin, the former of which is of especial importance in toxicology. These two alkaloids occur principally in the seeds of *Strychnos nux vomica* and of *Strychnos ignatii* (St. Ignatius' bean), in the wood of *Strychnos colubrina*, in the root-bark of *Strychnos tieuté* (the deadly upas tree, upas tieuté, or upas Radja). The leaves of *Strychnos nux vomica* contain brucin but no strychnin, while the root of *Strychnos icaia* contains strychnin but no brucin. Neither strychnin nor brucin are found in the seeds of *Strychnos potatorum*, *brachia*, *innocua*, *pseudoquina*, *spinosa*, *laurina*, or *monosperma*, while the bark of *Strychnos castelnæi*, *toxifera*, or *Crevauxii* is the common source of curare (curarin).¹

While the U. S. Pharmacopœia directs that the dried ripe seeds of *Strychnos nux vomica* shall yield not less than 2.5 per cent. of the alkaloids of nux vomica, and shall be used as the source of the pharmacopeial preparations, it is to be stated that brucin predominates over strychnin to a certain extent in this species, while in *Strychnos ignatii* a mere trace of brucin is found and, according to Moens,² nearly 1.5 per cent. of strychnin.

The seeds of nux vomica are "orbicular, nearly flat, occasionally irregularly bent, from 10 to 30 mm. in diameter, and from 4 to 5 mm. in thickness, very hard when dry; externally grayish or greenish gray, covered with appressed hairs giving it a silky luster, hilum indicated by a circular scar at the center of one of the flattened sides and connected with the micropyle at the edge by a ridge; internally showing a thin, hairy seed-coat and a large grayish-white endosperm at one end of which is embedded a small embryo with two broadly ovate, 5- to 7-nerved cotyledons; inodorous; taste intensely and persistently bitter. The powder is light gray; consisting chiefly of thick-walled endosperm cells containing globules of a fixed oil and a few aleurone grains, and fragments of strongly lignified, non-glandular hairs, the walls of the latter possessing large, circular, or long, slit-like pores. In the tissues of the adhering pulp occur a few small, nearly

¹ See Flückiger, Arch. der Pharm., 1892, cexxx, 343; Schmidt, Biochemisches Handlexicon, 1911, v, 165; Vanderkleed, Allen's Commercial Organic Analysis, 1912, vi, 441.

² Ztschr. f. Chem., 1862, 2 S., ii, 288.

spherical starch grains. *Nux vomica* yields not more than 3.5 per cent. of ash."¹

The official preparations of *nux vomica* are: (1) the extract, yielding not less than 15.2 per cent. nor more than 16.8 per cent. of the alkaloids of *nux vomica*; (2) the fluidextract, 100 mls. of which yield not less than 2.37 grams nor more than 2.63 grams of the alkaloids of *nux vomica*, and (3) the tincture, 100 mls. of which yield not less than 0.237 gram nor more than 0.263 gram of the alkaloids of *nux vomica*.

STRYCHNIN

Strychnin is the most important, both therapeutically and toxicologically, of the alkaloids of the *Strychnos* group. It was discovered by Pelletier and Caventou² in 1818. Its chemical formula is $C_{21}H_{22}N_2O_2$. In spite of the large amount of work done, especially by Tafel and by Leuchs and his students,³ the structural formula is still unsettled.

Strychnin is a monacid, tertiary base combining with one equivalent of acid to form salts. According to Tafel, it is an inner anhydrid of an imino-carboxylic acid (strychnic acid), which appears to contain two carboxyl groups, one of which is neutralized by the basic nitrogen, while the other gives to strychnin its acid character. Strychnin is distinguished as an alkaloid of stable composition, resisting various ordinary decomposing influences further than most organic compounds while still capable of very decisive chemical reactions. It occurs in colorless, transparent, prismatic crystals (of the rhombic system) or as a white crystalline powder; odorless, permanent in the air. It is very intensely and persistently bitter in taste, the bitterness being manifest in extremely dilute solutions. One gram of strychnin dissolves in 6420 mls. of water, 136 mls. of alcohol, 5 mls. of chloroform, and in 180 mls. of benzene at 25° C. (77° F.); also in 3100 mls. of boiling water, and in 34 mls. of boiling alcohol; very slightly soluble in ether. It crystallizes from benzene in octahedral crystals or well-formed crystals may be obtained by the gradual addition of water to the alcoholic solution, a fact of importance in the identification of this alkaloid in toxicologic examinations. Its saturated solutions are alkaline to litmus and are levorotatory. Its melting-point, when heated in small amounts, is 268° C. (514.4° F.), according to Löbisch and Schoop and confirmed later by Vanderkleed,⁴ although Stoehr and, later, Beckurts state this to be 265° to 266° C. (509° to 510.8° F.). It is precipitated from solutions of its salts by the general alkaloidal reagents,

¹ U. S. Pharmacopoeia, 9th Rev., 1916, p. 281.

² Ann. de chim. et de phys., 1819, 2 S., x, 142; Ibid., 1819, 2 S., xii, 113; Ibid., 1824, 2 S., xxvi, 44.

³ In this connection see Tafel, Ann. der Chem., 1892, cclxiv, 33; Ibid., 1892, cclxviii, 229; Ibid., 1898, ccc, 285 and 302; Tafel and Moufang, Ibid., 1899, ccciv, 49; Leuchs, Ber. d. d. chem. Gesellsch., 1908, xli, 1711; Leuchs and Schneider, Ibid., 4393; Ibid., 1909, xlii, 2494 and 2681; Leuchs, Ibid., 1914, xlvii, 536; Leuchs and Schwabel, Ibid., 1552; Leuchs and Bendixsohn, Ibid., 1919, liiB, 1443; Leuchs and Hintze, Ibid., 2195; Ciusa, Atti accad. Lincei, 1919, ii, 185; Chem. Abs., 1920, xiv, 2172.

⁴ Löbisch and Schoop, Monatsh. f. Chem., 1888, ix, 858; Vanderkleed, Allen's Commercial Organic Analysis, 1912, vi, 442.

picrolonic acid being especially valuable as a purifying reagent. It is precipitated by the fixed alkali hydroxids and carbonates, and is not readily soluble in excess of these reagents, although ammonia undoubtedly dissolves the precipitate when in excess to a more or less extent.

Strychnin Nitrate ($C_{21}H_{22}N_2O_2HNO_3$).—This official salt of strychnin occurs in colorless, glistening needles, or as a white, crystalline powder; odorless, permanent in the air. Even very dilute solutions of this salt are extremely bitter. One gram of strychnin nitrate dissolves in 42 mls. of water, 150 mls. of alcohol, 50 mls. of glycerin, and in 105 mls. of chloroform at 25° C. (77° F.); also in 9 mls. of boiling water, and in 77 mls. of alcohol at 60° C. (140° F.); insoluble in ether. Its saturated aqueous solution is neutral or only slightly acid to litmus and is levorotatory.

Strychnin Sulphate ($C_{21}H_{22}N_2O_2$) $_2$ H $_2$ SO $_4$ +5H $_2$ O.—This salt of strychnin is also official and occurs in colorless or white prismatic crystals, or as a white crystalline powder; odorless, and efflorescent in dry air. Its solutions are intensely bitter. One gram of the sulphate dissolves in 32 mls. of water, 81 mls. of alcohol, and in 220 mls. of chloroform at 25° C. (77° F.); also in 7 mls. of boiling water, and in 26 mls. of alcohol at 60° C. (140° F.); freely soluble in glycerin; insoluble in ether. Its saturated aqueous solution (1 in 50) is neutral or only slightly acid to litmus.

Symptoms of Poisoning by Strychnin or Nux Vomica.—The symptoms begin in many cases in ten or fifteen minutes after the poison is taken, but they have been known to begin immediately, and in other cases they may be delayed for an hour and even longer, there being in such cases an initial period of nervous excitation without violent symptoms (see p. 21 as to causes of difference in the time of onset of symptoms). Usually the first symptoms are a sense of tightness of the chest, stiffness of the neck, slight shudderings, and a feeling of impending calamity, drawing of the hands and feet, and, ere long, quite a sudden and violent tetanic convulsion, in which there are extension of the legs, arching of the feet, with the head drawn back, sometimes so that the body rests upon the heels and the back of the head (opisthotonos, which may be replaced by emprosthotonos or by pleurosthotonos), the arms extended or drawn tightly across the chest, the face fixed in a grin, the eyes staring, and the muscles of respiration so stiffened that suffocation seems to be threatened.¹ During the paroxysm the pulse is weak and irregular, the countenance is livid, the pupils are dilated, and frequently foam appears at the mouth. The duration of the convulsion is from half a minute to several minutes; the interval until the next convulsion is from a few minutes to half an hour. The number of spasms varies from one to ten or more, death sometimes occurring during the first spasm. In the interval the muscular rigidity nearly or quite disappears, there is general relaxation, a cold perspiration covers the surface of the body, and there are contraction

¹ See Repiso (Siglo Médico, 1920, lxxvii, 748) for an auto-observation of his symptoms following the taking of 10 cg. of strychnin by mistake for quinin.

of the pupils and a sense of weariness, the patient sometimes falling asleep. The access of another paroxysm is not infrequently preceded by a feeling of anxiety and sensitiveness, and appears to be brought on by any sudden movement or sound to which the patient is exposed. For the most part the mind is clear and steady, although oppressed during the paroxysm. Vomiting is not usual as a symptom, but it has been observed in some cases, as have also pain in the stomach and other signs of irritants.

Strychnin Poisoning Distinguished by Its Symptoms.—So distinctive are the usual symptoms in poisoning by strychnin that when they run an ordinary course and have been carefully observed, they can be relied upon quite fully for diagnosis. It is always a necessary inquiry, however, as to whether or not the symptoms observed may be due to some disease. Tetanus especially, also chorea, epilepsy, and uremic and puerperal convulsions, have been claimed to present symptoms liable to be mistaken for those of strychnin poisoning. In regard to these diseases the statements of Haines,¹ drawn from very extensive experience, are so valuable that they are here quoted entire: "All of these [the diseases just named] with the exception possibly of tetanus differ so essentially in their manifestations from strychnin poisoning that they could not possibly be confounded by a competent observer. The different forms of tetanus do in some respects resemble strychnin poisoning, yet there are such well-marked differences between them that, after careful examination, they should never be mistaken for each other. In both, it is true, there are violent tonic spasms which are strikingly similar, but in almost all other respects they are unlike. In tetanus we almost always have a history of an injury, and the disease usually comes on gradually and progresses slowly to a fatal termination, a number of days generally elapsing between the onset of the disease and death, while in strychnin poisoning there is no antecedent injury and the manifestations appear suddenly, almost without warning, and progress rapidly to a fatal termination; in tetanus the muscles first affected are generally those of the back of the neck, and those of the jaw are early invaded, producing persistent lockjaw, while in strychnin poisoning either the muscles of the extremities are first affected, and those of the neck and jaw last attacked, or the entire muscular system is thrown into a spasm almost, or quite, simultaneously; in tetanus there is usually considerable persistence of the muscular rigidity, even between the severe spasms, and opisthotonos or some other perverted position of the body is generally permanent, while in strychnin poisoning there is almost always complete relaxation between the spasms, and the opisthotonos, which may have been very marked during the attack, entirely passes away; in tetanus the temperature is generally somewhat elevated beyond the normal, while in strychnin poisoning it is not usually affected.

"There are, it is true, occasionally marked exceptions to the above differences, one case being recorded in which tetanus proved fatal in

¹ Hamilton's Legal Medicine, 1894, i, 449.

twelve hours after the first twitchings, another within an hour and a half after the first convulsion; on the other hand, a case of strychnin poisoning is recorded in which death occurred after a lapse of eighteen hours, and several cases are known in which repeated small doses of the poison have been administered in such a way as to extend the symptoms over a period of several days. So also in tetanus, cases are occasionally seen in which little or no increase of temperature is found, while in poisoning by strychnin the temperature is sometimes elevated. In spite, however, of these irregularities both in strychnin poisoning and in tetanus, a competent observer will rarely have difficulty in distinguishing the two, the difference in the order in which the muscles are attacked and the marked dissimilarity in the condition of the patient between the spasms generally sufficing to establish the exact character of the derangement."

Period When Fatal.—In the majority of fatal cases death occurs in from one to three hours; cases of death in ten minutes and in fifteen minutes and a case of death in eleven hours are given by Haines. If life is prolonged for five or six hours, recovery is probable. Of 57 cases of strychnin poisoning collected by Falck, 35 per cent. were fatal.¹

Fatal Quantity.—One-half grain (0.032 gm.) of strychnin or one of its salts is a poisonous quantity and liable to prove fatal. This amount has proved fatal in 2 cases, in both of which the dosage was accurately fixed. One of these cases was the death in five hours of a woman aged twenty-two from the administration of $\frac{1}{2}$ grain of strychnin through the mistake of a hospital nurse,² while the other is the case of Dr. Warner, who took $\frac{1}{2}$ grain of strychnin dispensed by mistake for morphin,³ and died in about fourteen minutes; $\frac{1}{4}$ grain (0.016 gm.) is reported⁴ to have caused the death of a woman of thirty-six years in one and three-quarter hours after it was taken. Several deaths have been reported from about $\frac{3}{4}$ grain,⁵ and also from 1 grain.⁶ While the minimum lethal dose of strychnin may be stated to be about $\frac{1}{2}$ grain for an adult, yet the *average fatal dose* for man, for internal administration, amounts to $1\frac{1}{2}$ or $1\frac{3}{4}$ grains (0.1 or 0.12 gm.). Certainly there would be a larger percentage of recoveries from the effects of $\frac{1}{2}$ grain of this poison than from the effects of 2 grains, irrespective of treatment. On the other hand, recovery has been reported following the taking of 9, 15, 19, 20, 27, 32, and 40 grains.⁷ In these cases it is

¹ Kobert, *Intoxikationen*, 1906, ii, 1154.

² Jones, *Lancet*, 1856, ii, 291 and 302.

³ Boston Med. and Surg. Jour., 1847, xxxvi, 209; Brit. Med. Jour., 1847, iii, 105; Woodman and Tidy's *Forensic Medicine and Toxicology*, 1877, p. 313.

⁴ Medical Times and Gaz., London, 1854, viii (n. s.), 376.

⁵ Watson, *Lancet*, 1846, i, 73; Ogston, *Ibid.*, 1856, i, 428; Socquet, Ogier, and Balthazard, *Ann. d'hyg.*, 1907, 4 s., vii, 523.

⁶ Dill, *Lancet*, 1873, ii, 533; De Courcillon, *Med. Arch.*, 1869, iii, 31.

⁷ In this connection see Lee, *Med. Bull.*, 1883, v, 82; Parker, *Med.-Leg. Jour.*, 1884, ii, 375; Berry, *Phila. Med. Reg.*, 1887, i, 566; Conner, *Ohio Med. Recorder*, 1879, iv, 12; Gray, *Brit. Med. Jour.*, 1880, i, 486; Davis, *Cinc. Med. and Dent. Jour.*, 1886-87, ii, 65; Niedner, *Charité Ann.*, 1905, xxix, 26; Wilson, *Amer. Jour. Med. Sci.*, 1864, n. s., xlviii, 70.

to be remembered, however, that emetics had been given. The results of any poisonous dose is governed by the product of a considerable number of factors, of which the dose is but one. Some cases have been reported, which indicate a cumulative action following repeated doses of strychnin.¹

Treatment of Poisoning by Strychnin.—1. The stomach should be cleaned out at once by the siphon tube or stomach-pump or by emetics and water-drinking. The muscular spasms often interfere with the introduction of the tube, and the inhalation of chloroform is to be hastened to abate the spasms as soon as possible, so that the stomach can be washed out. Solution of iodine, finely powdered charcoal,² or tannic acid may well be given at first to diminish the solubility of the alkaloid while it is being removed from the stomach. Apomorphin hypodermically is advised as an emetic (Kobert).

2. The inhalation of chloroform during the paroxysms and the administration of chloral hydrate by the mouth or hypodermically during the intervals are valuable remedial measures.

3. "The patient should be kept as quiet as possible; all strangers should be excluded from the room, direct drafts of air should be shut off, and loud noises, such as those produced by the slamming of doors, stamping of feet, etc., should be prevented. For the same reason as little medicine as possible should be given internally, as the mere raising of the head or touching of the lips may cause a convulsion."³

4. Following the work of Meltzer and of Meltzer and Auer⁴ on the control of tetanic convulsions, Githens and Meltzer⁵ have found that animals given a twice lethal dose of strychnin could invariably be saved by the use of intratracheal ether anesthesia plus the intravenous administration of considerable quantities of Ringer's solution (sodium chlorid, 9 gm.; calcium chlorid, 0.24 gm.; potassium chlorid, 0.42 gm.; sodium bicarbonate, 0.2 gm.; water, 1000 c.c.), the ether controlling the convulsions while the Ringer's solution hastened the excretion of the alkaloid. Cutler and Alton⁶ have found that magnesium sulphate was of use in controlling cases of strychnin poisoning. Following the recommendations of Meltzer as applied to cases of tetanus, these workers advise the use of 1 c.c. of 25 per cent. solution of magnesium sulphate to each 20 pounds of body weight in adults (and one-half the dose in young children) administered intraspinally. Should this not control the convulsions, a small amount of ether may be used. To

¹ Booth, *Med. Times and Gaz.*, 1856, xiii, 35; Pereira, *Mat. Med.*, 1872, 656; Dutger, *Med. and Surg. Reptr.*, 1865, xiii, 2; Hunter, *Med. Times and Gaz.*, 1867, ii, 5; Greenwood, *Lancet*, 1856, i, 654; Meier, *Berl. klin. Wehnschr.*, 1905, xlii, 1225; Clark, *Chicago Med. Times*, 1910, xliii, 109.

² See Sabbatani, *Bull. de sc. med. di Bologna*, 1909, ix, 360.

³ These directions of Haines (*Hamilton's System of Legal Medicine*, 1894, i, 451) are based upon sound pharmacology.

⁴ Meltzer, *Med. Record*, 1905, lxviii, 965; Meltzer and Auer, *Amer. Jour. Physiol.*, 1905, xiv, 366; *Ibid.*, 1906, xv, 387; *Ibid.*, 1906, xvi, 233; *Ibid.*, 1906-07, xvii, 313; *Ibid.*, 1908, xxi, 400; *Ibid.*, 1908-09, xxiii, 141; Meltzer, *Jour. Amer. Med. Assoc.*, 1916, lxvi, 931. See also Blake, *Surg., Gynec., and Obs.*, 1906, ii, 541.

⁵ *Jour. Pharm. and Exp. Therap.*, 1911, ii, 357.

⁶ *Jour. Exp. Med.*, 1917, xxv, 83.

hasten the excretion of the alkaloid, 200 to 300 c.c. of salt solution should be given intravenously. Should the convulsions return, they advocate repeating the dose of magnesium sulphate, always taking the precaution to keep the head elevated. In case of an overdose of magnesium salts, 2.5 per cent. solution of calcium chlorid should be used, Meltzer's apparatus for intrapharyngeal insufflation being ready at hand. Jona and Januschke¹ recommend adrenalin as an emergency treatment in cases of strychnin poisoning. Tizzoni and Perucci² have shown that both cholesterol and antitetanic serum may prevent the toxic action of strychnin, but by different mechanisms. When suitable mixtures of cholesterol and strychnin are injected, symptoms of poisoning do not develop, but a second injection of strychnin in another part of the body gives rise to symptoms. If, however, the second injection of strychnin be made near the site of the first injection of the mixture of cholesterol and strychnin, symptoms do not develop for the reason that the cholesterol remaining at the site binds the strychnin and slows the absorption. If a mixture of strychnin and antitetanic serum be injected subcutaneously, symptoms of strychnin poisoning develop, the strychnin being absorbed much more rapidly than the serum. If, however, the strychnin be injected subcutaneously and the serum intraperitoneally, the absorption of the serum is rapid enough to prevent the origin of symptoms when the strychnin reaches the central nervous system.³

5. If respiration is much diminished by the spasm, pure oxygen may be added to the air inhaled by the patient. Let it be borne in mind that the course of the poisoning is a short one, and if the patient can be carried through this period, he will recover.

Statistics.—Cases of strychnin poisoning have been relatively numerous in the past years, the majority of them apparently being of suicidal nature. In 1856 Husemann collected 56 cases, Schauenstein 200 cases up to 1868, Falck 57 cases for the years 1869 to 1880, Koppel 116 cases from 1880 to 1889. In 1911 Witthaus collated 663 cases of strychnin poisoning, of which 313 (47.3 per cent.) were suicidal; 189 (28.5 per cent.) were accidental; 134 (20.1 per cent.) homicidal; 27 (4.1 per cent.) of unknown type. Only 63 of these cases were in children less than ten years of age. According to the U. S. Census Report for the 1910 Census (see Wilbert, *Pub. Health Reports*, No. 330, 1916), strychnin poisoning was the cause of death 210 times, 113 cases suicidal, and 97 accidental. It is to be remembered that many cases of poisoning escape collation, owing to the fact that these cases do not find their way into the general literature, being reported only in the court records, or not investigated at all.

¹ Jona, *Intercolon. Med. Jour.*, Australasia, 1909, xiv, 342; Januschke, *Wien. klin. Wehnschr.*, 1910, xxiii, 284.

² *Ann. de l'Inst. Pasteur*, 1919, xxxiii, 722.

³ See Giribaldi, *Gazz. d. osp.*, 1919, xl, 1084, for a discussion of the antidotal effect of sodium chlorid.

CASES OF POISONING BY STRYCHNIN

CASE 1.—A dose of $\frac{5}{16}$ grain (0.02 gm.) of strychnin phosphate was taken by a man twenty-nine years of age. The respiration was almost suspended, the pulse small, soft, and too rapid to count, and the skin warm. The treatment was by $\frac{1}{2}$ ounce (14 gm.) of potassium bromid. The patient recovered.¹

CASE 2.—Three-fourths grain (0.049 gm.) of strychnin was taken by a woman of fifty years. There were convulsions; the body became perfectly rigid; the pulse was rapid. Under treatment by potassium bromid and chloral the patient recovered.²

CASE 3.—A dose of 0.77 grain (0.05 gm.) of strychnin nitrate was taken by a man of forty-one years. Symptoms: trismus, convulsions, stiffness of limbs, head bent back, without complete opisthotonos, the pulse 140 to 160, the respiration loud and labored. Treatment: potassium bromid and hypodermic administration of morphin. Recovery.³

CASE 4.—A dose of $\frac{3}{4}$ grain (0.049 gm.) of strychnin was taken by a woman of thirty-five years. There were spasms, pains in the legs, and a semidelirious state. Treated with apomorphin hypodermically and with chloroform inhalation, the patient recovered.⁴

CASE 5.—A dose of only $\frac{1}{16}$ grain (0.019 gm.) of strychnin arsenate was taken by a man of twenty-one years, with resulting clonic convulsions and opisthotonos. There was treatment with morphin hypodermically and by inhalation of chloroform. The patient recovered in five days.⁵

CASE 6.—A woman of twenty-five years took 2 grains (0.13 gm.) of strychnin. There were spasms, extreme opisthotonos, eyes turned up and divergent, the right pupil contracted and the left one dilated, the lower jaw firmly set, the respiration at one time being suspended for a minute and a half. Under treatment the patient recovered.⁶

CASE 7.—A man of thirty years took 6 grains (0.4 gm.) of strychnin. He suffered violent paroxysms. Treated with chloral hydrate, both hypodermically and by the mouth, the patient recovered.⁷

CASE 8.—A youth of eighteen years took 5 grains (0.325 gm.) of strychnin. Symptoms: convulsions, the face cyanosed, no radial pulse, the eyes blood-shot, the pupils of the eye dilated. Treatment: emetics and chloral hydrate by the mouth. Recovery.⁸

CASE 9.—A woman of fifty-six years took 4 grains (0.26 gm.) of strychnin. Symptoms: convulsions, lividity of the face, pulse 100. Treatment: emetics and hypodermic administration of morphin and atropin. Recovery.⁹

CASE 10.—A woman of twenty-eight years, poisoned by an unknown quantity of strychnin, suffered spasms with complete opisthotonos, and under treatment with atropin hypodermically, recovered.¹⁰

CASE 11.—A woman of twenty-three years, poisoned by 6 grains (0.4 gm.) of strychnin, suffered convulsions, became unconscious, was treated with hypodermic administration of chloral hydrate, and recovered.¹¹

CASE 12.—A healthy man of twenty-one years took from 13 to 18 grains of *liquor strychninae* (Br.) ($\frac{3}{4}$ grain—0.022 gm.—of strychnin) upon an empty stomach, and the symptoms which appeared in from fifteen to twenty minutes were clonic paroxysms, a cyanotic face, and dyspnea. Death followed in a short time. At the autopsy the muscles of the upper extremities, the jaws, and the eyelids were firmly contracted; the right side of the heart and the pulmonary vessels were filled with dark venous blood; the left side of the heart was empty; the brain was pale. The fluid in the stomach reacted to the test for strychnin, the urine was not examined.¹²

¹ W. B. Caley, *Lancet*, 1891, i, 18.

² E. Prideaux, *Ibid.*, 1881, i, 52.

³ Prinzing, *Schmidt's Jahrb. d. Med.*, 1890, ccxxv, 131.

⁴ Masson, *Brit. Med. Jour.*, 1894, ii, 808.

⁵ P. Bock, *Jour. de Méd. et de Chir.*, 1893, li, pl. vii, 97; *Schmidt's Jahrb. d. Med.*, cccxxix, 133.

⁶ S. Ott, *Med. News*, 1894, lxx, 270.

⁷ H. C. W. Jones, *Lancet*, 1889, ii, 166.

⁸ W. F. Wright, *Boston Med. and Surg. Jour.*, 1881, cv, 8.

⁹ J. N. Vojé, *Med. and Surg. Reporter*, 1879, xli, 525.

¹⁰ S. Buckley, *Amer. Jour. Med. Sci.*, 1874, lvii, 278.

¹¹ V. Fancion, *Schmidt's Jahrb. d. Med.*, 1884, cciii, 20.

¹² P. T. Adams, *Brit. Med. Jour.*, 1894, i, 300.

CASE 13.—A man took from 2 to 3 grains (0.13 to 0.2 gm.) of strychnin and died in one hour and a half. At the autopsy the abdominal and pectoral muscles were in a state of extreme tension, the blood was of a very dark color, the brain and upper part of the spinal cord were congested, as were also the meninges.

CASE 14.—A man took an unknown quantity of strychnin and died, after symptoms of the poisoning, in fifty-five minutes. At the examination of the body the blood was found to be dark, the brain, medulla, and upper part of the spinal cord were congested, as were also the lungs. About $\frac{1}{10}$ grain (0.006 gm.) of strychnin was recovered from the stomach, and about an equal quantity was recovered from the washings of the stomach obtained during treatment by the stomach-pump.¹

CASE 15.—A man of seventy-two years took an unknown dose of strychnin, suffered symptoms of the poisoning, and died. Forty-four hours after death there was persistence of rigor mortis, although a good deal of decomposition had occurred; no clots of blood were in the heart, and the thoracic muscles were pale. An abundance of strychnin was found in the stomach, along with 16 ounces (453 gm.) of partially digested food.²

CASE 16.—An infant was poisoned with nux vomica; three days after death cadaveric rigidity remained. Chemical analysis failed to reveal strychnin.³

CASE 17.—A person died from strychnin poisoning caused by two hypodermic injections of tincture of nux vomica. The brain was examined and strychnin found to be present.⁴

Another person died from hypodermic injections of nux vomica; analysis of the stomach yielded $\frac{1}{11}$ grain (0.042 gm.) of strychnin, and again the presence of the alkaloid in the brain was determined.⁵

CASE 18.—A man of twenty-four years, habituated to opium, died from a dose of strychnin. Ipecacuanha was used in the treatment. In the stomach no alkaloid was found; in the small intestine a little strychnin but no emetin or morphin; in the large intestine traces of strychnin, but neither morphin nor emetin; in 1033 grains (67 gm.) of blood from the heart, perhaps a trace of strychnin, but no emetin or morphin; in 2000 grains (130 gm.) of blood from the abdominal cavity a trace of morphin and undoubted traces of strychnin; in the liver, traces of strychnin but no emetin, the test for morphin lost; in the brain, traces of strychnin; in the second vomit, distinct evidence of strychnin, much emetin, but no morphin; in the third vomit, distinct proof of both strychnin and emetin, morphin uncertain; in the fourth and the fifth vomit, morphin distinct, but no emetin or strychnin.⁶

CASE 19.—A person died June 23, 1892, from poisoning by strychnin, as it appeared later. The body was exhumed after three hundred and eight days—that is, on April 25, 1893. Of the remains of the body, 5401 grains (350 gm.) were subjected to analysis for alkaloids—in fact, for strychnin. The final alkaloidal residue was twice purified by action of concentrated sulphuric acid for two hours on the water-bath. The tests for strychnin were obtained. Its quantity was estimated at $\frac{3}{8}$ grain (0.002 gm.).⁷

CASE 20.—A cat died fourteen minutes after receiving $1\frac{1}{2}$ grains (0.09 gm.) of strychnin. The alkaloid was found in the stomach, duodenum, upper small intestine, liver, kidneys, and bladder.⁸

¹ F. E. Marston, *Lancet*, London, 1886, ii, 442.

² L. Ogilvie, *Brit. Med. Jour.*, 1884, i, 1251.

³ *Amer. Jour. Med. Sci.*, 1879, lxxvii, 574; Führer, *Vrtljschr. f. ger. Med.*, 1876, n. F., xxv, 290.

⁴ Grandval and Lajoux, *Jour. Pharm. Chim.*, 1879 (4), xxx, 164.

⁵ *Ibid.*, 1892; *Repert. de Pharm.*, 1892, 304.

⁶ Dragendorff, *Organische Gifte*, 2d ed., 191.

⁷ W. A. Noyes, *Jour. Amer. Chem. Soc.*, 1894, xvi, 108.

⁸ Dragendorff, *Organische Gifte*, 191. For other cases of poisoning by strychnin see Burnett, *Medico-Pharm. Critic*, 1911, xiv, 378; Behrendt, *Ztschr. f. Med. Beamte*, 1911, xxiv, 118; Hewlett, *Physician and Surgeon*, 1912, xxxiv, 183; *Amer. Jour. Med. Sci.*, 1913, cxlvi, 536; Klessens, *Nederl. Tijdschr. v. Geneesk.*, 1913, i, 1779; Willführ, *Arch. f. Krim.-Anthrop. und Kriminalist.*, 1913, lii, 121; Trevisanella, *Liguria med.*, 1913, vii, 167; Bull, *South African Med. Rec.*, 1914, xii, 196; Glage, *Berl. tierärztl. Wehnschr.*, 1915, xxxi, 146; Graves, *Amer. Jour. Nursing*, 1915, xv, 1099; Palmer, *Med. Cor.-Bl. d. würtemb. Aerztl. Landesver.*, 1915, lxxxv, 314; Brown, *Jour. Amer. Med. Assoc.*, 1915, lxiv, 781; Bose, *Indian Med. Gaz.*, 1916, li, 347; Winklepleck, *Indiana State Med Assoc. Jour.*, 1920, xiii, 375; Rice, *Railway Surg. Jour.*, 1919-20, xxvi, 177.

Postmortem Appearances.—In a short time after death the muscles become extremely rigid, the joints fixed, the fingers closed, the feet arched, and sometimes the body bent backward. This extreme rigidity continues for a variable period—sometimes for a week and sometimes until after a good deal of decomposition has occurred. The brain and upper part of the spinal cord and their inclosing membranes are usually, although not always, overcharged with blood; the same congestion is frequently found in the liver and kidneys, and sometimes in the mucous membrane of the stomach. The heart is found to vary in respect to the amount of blood it retains (see Case 12). The *rigor mortis* is the most characteristic of the ascribed appearances; the others are not very distinctive nor very uniformly present.

Chemical Tests for Strychnin.—As already intimated the stability of this alkaloid, together with its decisive chemical and physiologic responses, enables it to be identified in tests of great delicacy.

1. **The Taste.**—The bitterness of strychnin is more intense than that of any other known substance. It can be perceived in a solution diluted to 600,000 or 700,000 parts. Wormley states that a drop of a 1 : 10,000 solution has a decidedly bitter taste, not usually masked by the presence of a very notable quantity of foreign matter. It is to be remembered that some persons do not possess the power of distinguishing bitter substances. For this reason the analyst must be certain that he himself is able to detect the bitter taste of strychnin before he makes this test, and, moreover, he should not be misled by the statements of others that a substance is not bitter.

2. **The Fading Purple Test.**—This test properly depends upon two facts—the one being that concentrated sulphuric acid at temperature of the water-bath purifies strychnin instead of coloring it; the other that the cold solution of strychnin in concentrated sulphuric acid, treated with certain oxidizing agents, gives an evanescent play of bright colors. The alkaloid is taken in solid state and dry, on a white porcelain surface, and the area of the test need not be over $\frac{1}{4}$ inch in diameter. A film of residue can be obtained in a separate narrow area by evaporating a drop of quite concentrated (chloroform) solution, and, if need be, several times repeating the evaporation on the same spot. The residue (or other solid portion) of the alkaloid is touched with the sulphuric acid at the point of a very narrow glass rod and left to dissolve. A small fragment of potassium dichromate is then brought by the glass rod into the liquid and slowly drawn through it at short intervals. The strychnin reaction is an appearance of changing colors—first a momentary deep blue, changing to deep violet, then to purplish red, cherry red, and finally, to orange or yellow (see Plate 5, No. 5). In the presence of small amounts of strychnin this play of colors may be so rapid that the bluish tints disappear almost in a flash. With larger amounts the purple tints may persist for quite a period before the fading appears. The oxidizing agents which have been used are potassium dichromate, cerosoceric oxid, manganese dioxid, lead peroxid, and potassium permanganate. Haines prefers cerosoceric oxid or the

dichromate. The writers have used the dichromate.¹ H. Letheby recommends the use of the electric current. The operator should make himself familiar with the behavior of the chosen oxidizing agent, both with sulphuric acid alone and with the sulphuric solution of strychnin. The change of color is slower with cerosoceric oxid than with the dichromate. If the residue (or fragment) to be tested has not been subjected to the action of concentrated sulphuric acid upon the water-bath, as directed under Separation from Tissues, page 584, then the sulphuric solution prepared as above is first heated on a water-bath, then cooled, and tested as above stated. A mere darkening by the sulphuric acid is likely to be due to impurity of non-alkaloidal matter. If not enough to interfere with the color test, such darkening may be disregarded. If there is too much darkening, the portion is treated for the purification of strychnin by hot concentrated sulphuric acid, as directed under Separation from Tissues, and then subjected to the color-test. A distinctive reaction can be obtained with about 0.000037 or $\frac{1}{27027}$ grain (0.0000025 gm.) of strychnin.²

With Mandelin's reagent³ (a 1 per cent. solution of ammonium vanadate in concentrated sulphuric acid) the color reaction is practically the same as the above, namely, a deep violet-blue, changing to a deep purple, and then to a cherry red, becoming yellow only on long standing. The color changes with this reagent are much slower than with the other oxidizing agents, with the possible exception of cerosoceric oxid, so that this test may be especially recommended for detection of very small amounts of strychnin.

The fading purple reaction of strychnin is prevented by the presence of much brucin or by much morphin. The absence of these alkaloids should be assured in the purification of the alkaloid for strychnin tests, as also the absence of sugar, or tissue substances in more than traces, etc. Solubility in chloroform or other volatile solvent and resistance to hot concentrated sulphuric acid are chief among the measures for purification. In removing brucin from a residue possibly containing both strychnin and brucin, dissolve the residue in about 2 c.c. of dilute sulphuric acid, add 2 drops of concentrated nitric acid, and let the mixture stand four hours. Render alkaline with excess of sodium hydroxid solution and extract thoroughly with ether. The residue from the ether will be brucin free or nearly so. Strychnin thus treated will give very satisfactory tests with concentrated sulphuric acid and potassium dichromate and with Mandelin's reagent. Instead of using this procedure, strychnin may be detected in the presence of brucin as follows: Dissolve the residue in concentrated sulphuric acid and

¹ See Prescott's Organic Analysis, 1887, 452.

² This limit was found when 1 c.c. of solution of strychnin was evaporated and the residue treated with 1 drop of sulphuric acid (see Organic Analysis, 452; Chem. News, 1886, liii, 78). Wormley found a limit at $\frac{1}{100000}$ grain (0.000007 gm.), and Hinsdale with cerosoceric oxid at $\frac{1}{100000}$ grain (0.0000007 gm.). For greatest delicacy the alkaloidal residue should be brought into an area much smaller than that of the residue of 1 c.c. in a single evaporation.

³ Pharm. Jahrb., 1883-84, 766; see also Kundrat, Ztschr. f. anal. Chem., 1889, xxviii, 709; Krug, Vrtljschr. f. ger. Med., 1914, 3 f., xlviii, 248.

add a trace of concentrated nitric acid. A red color indicates brucin. When the color has changed to yellow, add a fragment of potassium dichromate and stir. The mixture will become blue or reddish-violet if strychnin be present.¹

Various substances have been asserted to give nearly or quite the same fading color reaction as strychnin. The most of these substances are excluded at once by regarding the first condition of the test, the previous action of hot concentrated sulphuric acid, as already stated. Hydrastin, which is faintly colored yellow by sulphuric acid, treated with oxidizing agents, gives a play of colors not the same as that from strychnin.² Quebrachin is destroyed by heating with sulphuric acid (Haines). Curarin is colored by sulphuric acid, and is not very soluble in chloroform. Gelsemin gives a reddish-purple to cherry-red color without the initial blue or blue-violet, and the liquid assumes a green or bluish-green color which is never given by strychnin. Geissospermin shows a reaction with this test somewhat similar to that given by strychnin, but it is colored purple with nitric acid, while strychnin shows no color with this reagent.

The Lloyd Reaction of Morphin with Hydrastin in the Fading Purple Test.—In his popular novel, *Stringtown on the Pike*, published in 1900, Professor John Uri Lloyd introduces into the murder trial of Red Head, what has proved a feature of much chemical interest, a fallacy of the fading purple test, due to the combined reaction of two alkaloids, the one contained in golden-seal root and the other in laudanum. The writers are indebted to Professor Lloyd for a fine sample of the mixed alkaloids—hydrastin 9 parts with morphin 1 part. Tests of this mixture confirm results which had previously been obtained with hydrastin mixed with morphin and with hydrastin alone, in effect as follows: The mixture of hydrastin and morphin, treated on white porcelain with concentrated sulphuric acid and not heated, at first shows only a pale yellow color, gradually deepening as it stands. On adding a fragment of potassium dichromate there is a play of purple to maroon-red coloration. The colors do not fade, but they grow gradually darker and duller, so that in from fifteen to thirty minutes the color becomes nearly or quite uniform and of a dark brown, varying from the prevailing color of mahogany to that of black walnut wood when oil finished. Hydrastin alone, treated on white porcelain with concentrated sulphuric acid, gains a pale yellow color, the same result that is obtained with the mixture of hydrastin and morphin. If, now, the heat of a water-bath be applied, as recommended for the purification of strychnin, the liquid soon darkens and deepens, without any play of color, to a maroon-red and then mahogany-brown coloration. Later very dark particles of solid appear, due to the beginning of carbonization by the hot sulphuric acid. This action of hot sulphuric acid enables the operator to remove hydrastin, as well as ordinary tissue substances, from any strychnin in

¹ Autenrieth-Warren, *Detection of Poisons*, 4th ed., 1915, 96.

² A. B. Lyons, *Amer. Jour. Pharm.*, 1886, 3 s., xvi, 880; see also the next paragraph.

the residues under treatment. Hydrastin itself, the colorless alkaloid of *Hydrastis canadensis*, with the formula $C_{21}H_{21}NO_6$, crystallizes trimetric, and melts at $135^{\circ} C.$ ($275^{\circ} F.$). It is nearly insoluble in water, very freely soluble in chloroform, soluble in about 16 parts of benzol, about 84 parts of ether, and 120 parts of alcohol.¹

3. The Chromate Test.—When a drop of an aqueous solution of a salt of strychnin is touched with solution of potassium dichromate a yellow crystalline precipitate can be obtained, and the crystals are octahedral and dendroidal in form. While the octahedra are distinctive, the dendroidal crystals are, perhaps, more frequently obtained; dendroidal or brush-like aggregations may be formed from the dichromate itself. In applying this test to a portion of the extract from tis-

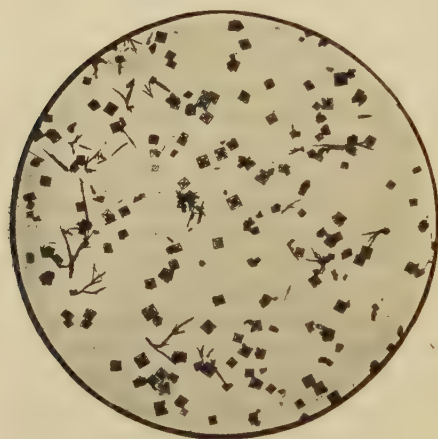


Fig. 57.—Strychnin with the dichromate.

sues, a few drops of the chloroform solution are evaporated upon a glass slide, the residue taken up with a drop of dilute acetic acid, and the excess of acid mostly dissipated, then the border of the liquid wetted with the dichromate solution and the mixture stirred, without unduly spreading it, at the point of a very narrow glass rod. The slow formation of a crystalline precipitate is promoted by slight concentration or by slight dilution. Any crystals obtained are examined under a microscope with a suitable power, comparing with a control test.

Fading Purple Test of the Chromate.—If the crystals of the chromate be obtained, they are to be gathered to a point on the glass slide and dried, then touched with concentrated sulphuric acid, when the play of fading colors will be obtained the same as in the direct color test.

4. Buc's Test.—Prepare a zinc amalgam as follows: Treat granular zinc with a little concentrated hydrochloric acid so as to clear the surface and pour off the acid. Cover the metal with 1 per cent. solution of tartar emetic (antimony and potassium tartrate), shaking occasionally during one hour. Add a saturated solution of mercuric chlorid (1 c.c. for every gram of zinc), and then add a few drops of concentrated hydrochloric acid. After thirty minutes pour off the solution and wash thoroughly with water and dry. The test is performed as follows: To the dried residue of the alkaloid or any of its salts, or to an aqueous solution (the volume of which should be about 0.5 c.c. or less) add 0.5 to 1 gram of the zinc amalgam and 0.5 c.c. of con-

¹ On the history of hydrastin see a part of an article by Prescott, Jour. Amer. Chem. Soc., 1899, xxi, 736.

centrated hydrochloric acid. If the amount of strychnin is very small, allow to stand fifteen or twenty minutes, less time being required with larger amounts. Pour off the solution from the zinc, taking care not to carry along any particles of the zinc. Add by drops a 0.02 per cent. solution of potassium ferricyanid, when a pink to rose-red color will indicate strychnin. Large amounts of other alkaloids and other organic substances will interfere with the test by reacting with the ferricyanid, but these interfering substances should not be present in a properly purified residue. The test indicates about 0.001 mg. of strychnin in the absence of interfering substances.¹

5. Malaquin's Test.—One c.c. of a very dilute solution of a strychnin salt (not stronger than 1 : 1000) is mixed with 2 c.c. of hydrochloric acid and 1 gram of granulated zinc. After two or three minutes at ordinary temperature, it is heated quickly to boiling, cooled, and poured carefully, so as to form a separate layer on to 2 c.c. of concentrated sulphuric acid contained in a test-tube. If strychnin be present a rose-red ring will be formed at the surface of contact of the two liquids and gradually the whole mixture will become rose red in color. On heating to boiling, the color is not changed but the mixture is rendered colorless by potassium sulphocyanate, ammonia, or sodium hydrogen sulphate in excess. This test will detect strychnin in a dilution of 1 to 1,000,000. According to Malaquin the only known alkaloid which might be mistaken for strychnin by this test is veratrin, but this is differentiated by the fact that when the mixture of sulphuric acid and the treated alkaloid be boiled, this is changed to a dirty yellow with veratrin, while with strychnin the red color remains unchanged.²

The Biologic Test.³—The frog is the animal to be taken. The aqueous solution of a salt of the alkaloid, not more than slightly acidulous,⁴ nearly purified when obtained by extraction from tissues or foods, is given to a small frog, either hypodermically into the lymph-sac immediately beneath the skin of the back at the root of the hind legs, or by blowing into the stomach through a small tube. The time is noted and the animal is put under a glass jar and observed. Tetanic spasms are caused by strychnin, the spasms being preceded by a period of uneasiness with accelerated respiration. Wormley obtained, with frogs of from 15 to 50 grains (0.98 to 3.3 gm.) in weight, from $\frac{1}{5000}$ grain (0.000013 gm.), distinctive symptoms in from ten to thirty minutes; from $\frac{1}{3000}$ grain (0.00013 gm.), symptoms in three or four minutes and death in from fifteen to thirty minutes. Kobert mentions $\frac{1}{30}$ grain (0.002 gm.) as a fatal dose for a frog. The paroxysms at first have remissions, and their return is hastened by agitation or vibration, as by striking on the table.

¹ Jour. Assoc. Off. Agr. Chem., 1919, iii, 193.

² Jour. Pharm. et Chim., 1909 (vi), xxx, 546.

³ This test is known under the name of Marshall Hall, who first suggested its use in forensic medicine, Lancet, 1856, i, 36 and 335.

⁴ This is an important point as a solution which is strongly acid may cause death of the animal with collapse due to acid poisoning without any symptoms of strychnin poisoning being observed.

Separation of Strychnin From Tissues, Foods, or Contents of the Stomach.—A weighed quantity of the material, or determinate fraction of the organ, finely divided if necessary, with water enough to make it into a free flowing mixture, is strongly acidulated with acetic or sulphuric acid,¹ and digested on the water-bath for about an hour, adding water to replace that evaporated. The mixture is strained hot, the liquid concentrated on the water-bath to about one-fourth its first volume, and to this reduced liquid, while hot, five or six times as much strong alcohol is slowly stirred in. A good deal of organic matter is precipitated by the alcohol, and this is to be filtered out, washing the precipitate with portions of alcohol of the same strength as that of the filtrate. The total filtrate is evaporated on the water-bath to a syrupy liquid, and this, when cold, is treated with enough water, slightly acidulated with acetic or sulphuric acid, to make it feasible to filter the whole, quite clear, into a separatory bulb or strong large test-tube, for shaking out with about an equal bulk of chloroform or other solvent immiscible with water.

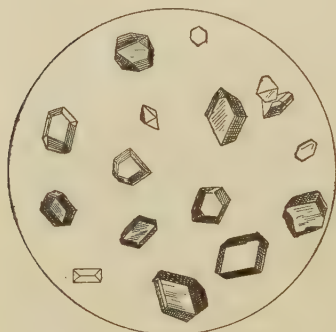


FIG. 58.—Strychnin crystals from benzene.

Directly before shaking out the liquid is made very slightly alkaline by addition of potassium or ammonium hydroxid solution. The shaking out is to be done thoroughly, but guarding against making an emulsion, and after drawing off the separated chloroform, the shaking out is repeated with a second and perhaps a third portion of the chloroform. If the solvent refuses to separate, ether may be added in volume equal to that of the chloroform, and this ether-chloroform solvent may be taken, in shaking out a second and a third time. Chloroform alone is

to be preferred, if it does not emulsionize too much. The united chloroformic portions, obtained quite clear, are gently evaporated in a porcelain dish. The residue, still containing a good deal of extraneous organic matter, will contain the strychnin, if present in the material operated upon. To purify the alkaloid further, the shaking-out with chloroform is repeated by taking up the residue with dilute acetic or sulphuric acid, filtering, adding the chloroform in the separatory tube, making alkaline, and going on as before, again evaporating the chloroform solution in a porcelain dish.

Almost always it is necessary to purify the residue further, and in case of strychnin there is a remarkable opportunity to do this by action of hot concentrated sulphuric acid. To do this, the dry residue is well moistened with sulphuric acid, 2 or 3 drops being usually sufficient,

¹ These directions are mainly those given by Haines, from his large experience, in Hamilton's Legal Medicine, vol. i, p. 456.

and the whole heated on the water-bath for an hour or two,¹ or to 120° C. (248° F.) for fifteen or twenty minutes in the drying oven. The blackened residue is now stirred with water, filtered and washed, made faintly alkaline, and shaken out with chloroform. The chloroform solution is sufficiently concentrated and then kept under a stopper, preferably in a small graduated cylinder. Small portions are taken with care for evaporation on porcelain, for the several chemical tests described above. Should the first residue by evaporation of a portion of the chloroform prove not sufficiently pure and colorless, the residue of the whole, or of a portion, may be further purified by another digestion with hot concentrated sulphuric acid as before.

For a quantitative estimation an aliquot part of the entire chloroform solution is thoroughly purified, its final chloroform solution evaporated on a small tared watch-glass, washed with a few drops of ice-cold water, dried, and weighed. It must be understood, however, that an alkaloid cannot be separated from tissue substances without loss.² The ratio of the loss of alkaloid to the weight of tissue material may be approached by a parallel control analysis, but it is doubtful whether sufficient data can be obtained to justify an estimation of the quantity of alkaloid in the entire body in a case of death from poisoning.

In the above process of extraction of strychnin from tissues, as also in the routine procedure of Dragendorff, it is to be remembered that a very decided positive error may creep into the gravimetric determination, owing to the possible presence of caffein in the residue as weighed. This error may not be at all evident in the qualitative examination, as caffein does not interfere with or simulate the reactions for strychnin. The amount of caffein present may be considerable, as it may have been given by the physician as such or in the form of coffee or tea in his treatment of the case, or may, indeed, have been taken by the subject himself before or at the time of the ingestion of the strychnin. Caffein is not readily soluble in the immiscible solvents used in the Dragendorff process, with the exception of chloroform and benzene, so that some of it would pass through the extraction of the acid solution by such solvents and appear later in the chloroform extract of the alkalized solution. According to Allen³ four treatments with chloroform usually effect the complete extraction of caffein from acidulated solutions, but it is desirable to agitate a fifth time, rendering the solution ammoniacal, or a loss of 1 to 2 mg. may occur. The possibility of such transference of 1 to 2 mg. of caffein to the strychnin residue must be borne in mind. Further, if such repeated chloroform extractions of the acid residue be made and the quantity of strychnin originally present be small, the chloroform may remove most of the strychnin from the acid solution and thus introduce a very marked negative error into the determination. Moreover, caffein cannot be

¹ As to formation of a strychnin-sulphonic acid under this treatment see Stoecher, *Ber. d. d. chem. Ges.*, vol. xviii, p. 3429.

² See Prescott's *Organic Analysis*, p. 461, or *Chem. News*, 1885, liii, 78; also Fuller, *Jour. Assoc. Off. Agr. Chem.*, 1919, iii, 188.

³ *Commercial Organic Analysis*, 1893, iii (pt. 2), 485.

removed from the field of action by treatment of the evaporated chloroform extracts with concentrated sulphuric acid in the heat. Allen¹ has shown that caffein was wholly unchanged when heated in the water-oven, even for several hours, with concentrated sulphuric acid. In order, therefore, to be certain of the removal of the extraneous caffein and to obtain accurate gravimetric results, the purified residue should be washed freely with ice-water, which will remove the caffein and, probably, a little of the strychnin, but the loss of strychnin will not introduce such an error as will the failure to remove the caffein which is possibly present. This same error may arise in the extraction of many other alkaloids.

Strychnin-like Ptomaines.—With strychnin, like some other alkaloids, one may possibly confuse certain putrefactive products obtained in the extraction processes, although the treatment of the residue with concentrated sulphuric acid will rule such derivatives out of consideration. However, in some cases, mistakes of identity have been reported.

At a trial for murder at Verona, Italy, Ciotto² obtained from the exhumed but only slightly decomposed body, an alkaloid that gave a crystalline precipitate with iodine and hydriodic acid, a red coloration with hydriodic acid, and a color test similar to that of strychnin with sulphuric acid and potassium dichromate and with other oxidizing agents. This substance was strongly poisonous, but in its action it differed materially from strychnin, inasmuch as it did not produce the tetanic convulsions that are so characteristic of this alkaloid. Ciotto was in doubt concerning the exact nature of this body, but pronounced it probably identical with strychnin. The tissue was submitted to Selmi for further investigation and for his opinion. Selmi³ ascertained that the substance that gave the color reaction was not crystalline, and that there was only the presumption of a bitter taste to it. He further convinced himself that many putrefactive substances give reactions similar to strychnin with iodine and hydriodic acid, and with hydriodic acid alone. He stated definitely that no ptomain known at that time gave the sulphuric acid dichromate reaction, which is similar in all respects to that shown by strychnin. Further, he held that the physiologic properties of this substance were such that it could not be strychnin.

Amthor⁴ obtained a ptomain by the Stas-Otto method, which passed from alkaline solution into benzene and into amyl alcohol, which was not crystalline, only faintly bitter, and with the fading-purple test gave a green color. Such reactions should not cause the faintest suggestion that strychnin was present, although at the time there was some doubt raised. Mecke⁵ obtained a faintly bitter, non-tetanzing ptomain, which gave the reaction with sulphuric acid and dichromate, but was colored red by sulphuric acid alone, yellow by Erdmann's

¹ Commercial Organic Analysis, 1893, iii (pt. 2), 478.

² Parte chimica di un Caso di Perizia, Padova, 1880, 39.

³ Sulle Ptomaine, Bologna, 1881, 224.

⁴ Cited by Baumert, Lehrb. d. ger. Chem., 2te. Auf., 1906, 353.

⁵ Pharm. Ztg., 1898, xliii, 300.

reagent, and with Fröhde's test a dirty violet, changing to olive and to green, which reactions should have ruled out any consideration of the presence of strychnin.

Ptomains giving reactions similar, but not identical, with those of strychnin and also causing tetanic symptoms, have been found in Italy in decomposed cornmeal. Lombroso and Dupre¹ showed that the color reaction resembled that of strychnin only in its initial stage, giving a blue color which passes to a dirty yellow without any appearance of the reddish tinges. Several such bodies have been noted in cornmeal, some of which cause narcosis and paralysis, while others produce the symptoms of nicotin poisoning and some those of the tetanic convulsions of strychnin.

From the above it will appear that none of the bodies isolated have given reactions, which should have been confused with those of strychnin if the totality of identifying tests had been properly considered. It is to be insisted upon that exact similarity in all respects be present if the color reactions are to be properly interpreted. Further, unless the chemical and biologic tests agree, strychnin cannot be definitely proved to be present. Wherever possible the biologic tests should be employed as a check upon the chemical tests, as in this way probability is increased to certainty.

Deposition of Strychnin in the Body.—Strychnin is eliminated unchanged to some extent by the perspiration, saliva, bile, and much more by the urine (Kobert), and not at all by the feces.² As a poison it has been recovered especially from the liver³ and the kidneys, and an unabsorbed remainder is generally to be found in the stomach and its contents. It has been found in the brain and in the blood (see Cases 14 to 20).

Occasionally the question arises in forensic cases as to whether the administration of remedial quantities of strychnin may lead to the deposition in the various organs of sufficient quantities of this alkaloid to permit of its isolation and identification. Norris, Gettler, and Haines (personal communication) studied this question by examining the organs of certain patients dying in Bellevue Hospital from disease and to whom known amounts of strychnin ($\frac{1}{30}$ gr. three or four times daily; one case $\frac{1}{60}$ gr. three times daily) had been administered for two or three days prior to death. In all cases studied strychnin was found in the liver and brain in quantities too small to permit of quantitative determination, but, nevertheless, in amounts sufficient to yield unequivocal chemical and biologic tests. The same results have been observed by Haines in connection with another forensic case of non-strychnin poisoning, in which strychnin had been administered as a remedial agent. It is evident, therefore, that the toxicologist should be on his guard as to the deductions to be drawn from the presence of a small amount of strychnin in the organs examined and that he

¹ Lo Sperimentale, 1876, xxxviii, 253, 385, 516.

² Hatcher and Eggleston, Jour. Pharmacol. and Exp. Therap., 1917, ix, 359.

³ See Weiss and Hatcher, Jour. Pharm. and Exp. Therap., 1922, xix, 419.

should learn, if possible, whether or not strychnin had been administered for therapeutic purposes.¹

Detection in the Body After Prolonged Periods.—Authorities agree that strychnin long resists decomposition in the body. Haines² states that he extracted it in a ponderable quantity from a body that had been buried for nearly twelve months (see also Case 19). Allen recovered strychnin from a stomach that had been preserved in alcohol for six years.³ Lesser⁴ detected strychnin in the completely mummified body of a woman three hundred and thirty-seven days after death, while Kratter⁵ discovered it in the body of a man, which had been buried five years and eight months and had been externally converted into adipocere.

Failure to Detect.—There are a considerable number of cases of death from undoubted strychnin poisoning in which competent chemists have been unable to find the alkaloid in the body. Haines⁶ states that he examined the stomachs of two children who died suddenly with all the symptoms of strychnin poisoning, etc., but could not obtain any indication of the poison in the analysis of either case (see Cases 16 and 18).

BRUCIN

A definition of this alkaloid is given under the general description of Strychnin, to which it is related in chemical constitution, botanic occurrence, and physiologic effect. Brucin ($C_{23}H_{26}N_2O_4$), a dimethoxystrychnin, is much less stable than strychnin itself, especially in resistance to oxidizing agents, and much less potent in effect as a poison, although similar in its action. The exact determination of the potency of brucin has been embarrassed by the difficulty of absolute exclusion of strychnin. Each of these alkaloids must be separated from the other in manufacture. Therefore an article of brucin obtained from an ordinary dealer is liable to contain enough strychnin to exert a sensible effect, and the impurity is the more likely to be overlooked because the color-test for strychnin is obscured by the presence of no more than an equal weight of brucin. A method of separation of strychnin from brucin should precede the test of the latter for the presence of the former. The nux vomica seeds contain both these alkaloids; the bark contains brucin with very little strychnin, and in the bark of some species of strychnos brucin is found without strychnin. Therefore in cases of poisoning by the crude drug it is desirable to assay it for content of brucin as well as for strychnin.

Brucin occurs as a bitter, white, odorless, crystalline powder, or as colorless, transparent, monoclinic prisms or shining leaflets, containing 2 or 4 molecules of water of crystallization. It melts in its water of hydration only a few degrees above 100° C. (212° F.), whereas the

¹ See also Arnesen, Norsk Mag. f. Laegevideusk., 1921, 82, 495.

² Hamilton's System of Legal Medicine, vol. i, p. 459.

³ Commercial Organic Analysis, 1912, vi, 459.

⁴ Vrtljschr. f. ger. Med., 1898, 3 F., xv, 270.

⁵ Ibid., 1907, 3 F., xxxiii, 131.

⁶ Hamilton's System of Legal Medicine, 1894, i, 459.

anhydrous base melts at 178° C. (352.4° F.). Brucin is more readily soluble than strychnin both in water and in alcohol. It is readily soluble in acetone, benzene, and chloroform, while it dissolves in ordinary ether, but is almost insoluble in absolute ether. Amyl alcohol dissolves it readily, but petroleum ether with difficulty. Its solutions are levogyrate, intensely bitter, and show a marked alkaline reaction. Chemically it is a monacid, tertiary base, being a dimethoxy derivative of strychnin. It forms readily crystallizable soluble salts.

Symptoms of Poisoning by Brucin.—Brucin resembles strychnin closely in action, but is much weaker and less toxic. Much of the reported study of the physiologic action of brucin must be regarded as somewhat uncertain owing to the contamination of the brucin used with strychnin. The symptoms of poisoning in man must be regarded as essentially those of strychnin, although one must make some reservation as to the convulsive seizures noted with strychnin, as these may not appear under the influence of brucin. While brucin may cause much the same symptomatology noted with strychnin, yet its action may be slower in appearing and much less intense. For interesting discussions as to the physiologic action of brucin, as compared with strychnin, see the references given below.¹

Fatal Amount.—The lethality of brucin, especially as compared with strychnin, has been studied by several with varying results, due probably to the fact that the brucin with which many of them worked was not pure. Thus Andral² found brucin to have one-twelfth the strength of strychnin, while Magendie states this ratio to be 1 : 24. Falck,³ in his experiments on rabbits injected subcutaneously with brucin nitrate in varying doses, showed that the minimum lethal dose for rabbits was 23 mgs. per kilo, while under the same experimental conditions, that of strychnin was 0.6 mg. per kilo.; in other words, the ratio of the lethality of strychnin to brucin was $38\frac{1}{3} : 1$. He noted three stages in the symptomatology of the brucin action: First, the respiration was quickened; secondly, there were tetanic convulsions, trismus, opisthotonos, oppressed respiration, and dilated pupils; thirdly, the animal was moribund. He found that strychnin killed 3.06 times more quickly than brucin, the intensity of its action relative to that of brucin being as 117.4 : 1. Reichert⁴ observed that brucin was from forty to fifty times less powerful than strychnin as a convulsant, was more poisonous to the sensory nerves, and was less rapidly absorbed. On the other hand, Husemann⁵ reports the toxicity of brucin as being

¹ Brunton, *Jour. Chem. Soc.*, 1885, xlvii, 143; Mays, *Jour. Physiol.*, 1887, viii, 391; Von Wittich, *Virchow's Arch. f. Path. Anat.*, 1858, xii, 426; Liedtke, *Dissert.*, Königsberg, 1876; Husemann, *Arch. f. exp. Path. u. Pharm.*, 1878, ix, 429; Braatz, *Dissert.*, Kiel, 1891; Rothmaler, *Dissert.*, Kiel, 1893; Todtenhaupt, *Dissert.*, Königsberg, 1904; Robins, *Philadelphia Med. Times*, 1879, ix, 228; Lautenbach, *Ibid.*, 521; Monnier, *Arch. des Sci. Phys. et Nat.*, 1881, v, 57; and Santesson, *Arch. f. exp. Path. u. Pharm.*, 1895, xxxv, 57.

² Cited by Husemann, *Arch. f. exp. Path. u. Pharm.*, 1878, ix, 429; Magendie, *Jour. de Physiol.*, iii, 267; Taylor gives these figures as Magendie $\frac{1}{2}$ and Andral $\frac{1}{6}$.

³ *Vrtljschr. f. ger. Med.*, 1875, N. F., xxiii, 78.

⁴ *Med. News*, 1893, lxii, 369.

⁵ *Arch. f. exp. Path. u. Pharm.*, 1878, ix, 429.

only eight to nine times less powerful than strychnin, a result that is probably due to his impure brucin.

It is a difficult matter to give an idea as to the fatal dose of brucin, as no clearly established fatal cases (see succeeding paragraph) are to be found in the literature. If one accepts the results of animal experimentation and attempts to convert them into figures for man, it is probable that 20 to 25 grains (1.29–1.62 gm.) would be about the least fatal dose of brucin.

Cases of Poisoning By Brucin.—A search of the literature has failed to reveal but one authentic case of true brucin poisoning. It is true that there are some cases cited, which have been assumed to be due to brucin, but a study of the reports from the original sources shows that none of these should be attributed to brucin any more than to other poisons taken at the same time. Thus, Christison¹ cites the case of a boy and of Professor Marc of Paris, the former taking some form of false angostura bark, while the latter took three-fourths of a liqueur glass of an infusion of false angostura by mistake. In this latter case the symptoms resembled those of strychnin continuing two hours, after which they abated under the use of ether and laudanum with recovery. It is just as probable that the symptoms noted in these cases arose from strychnin as brucin, as the false angostura bark contains both of these alkaloids. Taylor² mentions the case of Dr. Edwards of Liverpool, as being a warning to physicians of the toxic action of brucin, but gives no data regarding the case. Casper³ cites 3 cases of poisoning by arsenic and brucin. These were the cases of 3 children in one family, who took sick at intervals of some hours apart after eating (supposedly) pieces of bread and sausage which had been treated by the rat-catcher, who confessed that he employed a paste composed of butter, minced meat, arsenic, and lamp black. In his chemical examinations Casper found brucin, although his identification was limited to the nitric acid test. In his first examination of the bread and meat he did not find arsenic, but in a later examination he was able to show the presence of arsenic. He states that "these substances, on the other hand, contained brucin, which justifies the assumption of their having been mixed with powdered nux vomica." If nux vomica were actually used, a point which was denied by the person who prepared the paste put upon the bread and meat, then strychnin was present as well as brucin and the cases need not be ascribed to brucin any more than to strychnin. A further point of interest in these cases is that neither brucin or arsenic was found in any of the three bodies, which were examined by Casper. It is said that the symptoms outlined in these cases would seem to point to botulism much more than to poisoning either with arsenic or brucin.

Aside from the above assumed cases of poisoning by brucin, none

¹ A Treatise on Poisons, 1st Amer. ed., 1845, 692. With reference to the case of Prof. Marc, he cites *Jour. de Pharm.*, ii, 507.

² On Poisons, 3d Amer. ed., 1875, 669.

³ Handbook of Forensic Medicine, 1862, 102.

of which appear to be authentic cases of true brucin poisoning, the literature reveals one non-fatal case of brucin poisoning. Sozinskey¹ reports the following: Two grains of brucin were taken by a middle-aged vigorous man. He was seen by the physician two hours after taking the drug. At that time the patient showed dread pictured on his face, and was holding by the arms of the chair lest he should fall into convulsions. Symptoms noted were essentially those of strychnin. Treatment with emetics and repeated doses of chloral and $\frac{2}{5}$ grain of morphin. In five hours after taking the drug, the convulsive state had largely disappeared and recovery was rapid.

It will thus be seen that brucin should be regarded as a toxic drug, but that its effects are such that a large dose is required to produce fatal effects. Caution must, however, be used in the taking of alcoholic preparations which have been denaturized with this drug.

Chemical tests for brucin are as follows: To a colorless residue to be tested, on a white porcelain surface, add a drop of concentrated sulphuric acid. With this brucin itself gives no color. A very little nitric acid is now added on the point of a sharp glass rod, when a blood-red color reveals brucin. The test may be varied by treating the residue first with dilute nitric acid, then with concentrated sulphuric acid. Treatment of the residue with nitric acid gives a blood-red color, which on warming gently changes to yellowish red and finally to yellow. If a few drops of a freshly prepared dilute stannous chlorid solution, or of colorless ammonium sulphid be now added, an intense purple color appears. This color is destroyed by excess of nitric acid so that the smaller the quantity of this acid added the more likely is the test to succeed (see Plate 5, No. 2).

Blyth's Test.²—If to a solution of brucin in strong alcohol a little methyl iodid is added, at the end of a few minutes circular rosettes of crystal groups appear, which are composed of methyl brucin iodid. Crystals identical in shape are also obtained if an alcoholic solution of iodine, or hydriodic acid with iodine, be added to an alcoholic solution of brucin. A solution of strychnin gives with methyl iodid no similar reaction and, further, strychnin in alcoholic solution, mixed with brucin, in no way interferes with the test.

To test for strychnin in the presence of brucin, treat the residue with concentrated sulphuric acid, then with a very little nitric acid, and after the red color has changed to yellow, add a minute fragment of potassium permanganate or of potassium dichromate. A blue or blue-violet color, the "fading purple," indicates strychnin. In this test the interference of the brucin is avoided by its decomposition or conversion into derivatives. Keller estimates strychnin in a mixture with brucin after decomposing the latter, by digesting the dry alkaloids, first with sulphuric acid of 10 per cent. strength, then in the cold with one-tenth as much nitric acid of specific gravity 1.42, leaving for one and one-half hours in the cold. In the "fading purple" test for strychnin

¹ Med. and Surg. Reporter, 1882, xlvii, 194.

² Poisons: Their Effects and Detection, 4th ed., 1906, 351.

the interference of brucin is diminished by using the permanganate as an oxidizing agent, when the brucin is decomposed to a greater extent than results from the dichromate.

In the separation of brucin from tissues and foods advantage is to be taken of the fact that brucin is much more soluble in alcohol than is strychnin. Absolute alcohol is a good separative solvent for free brucin, as is also alcohol of 50 per cent. strength.¹ Brucin has less resistance to decomposition by oxidizing influences than has strychnin, and must not be heated with concentrated sulphuric acid on the water-bath, as directed for the last-named alkaloid.

THE VERATRUM ALKALOIDS

General Description.—The several species of *Veratrum* contain a number of similar alkaloids whose chemistry and relations have been much confused, and are still more or less obscure. The literature of this subject is quite confusing, as different workers have applied the term "veratrin" to substances which are quite different in both chemical and physical properties. Indeed, the various pharmacopeias employ the designation "veratrin" for a mixture of alkaloids with no attempt at differentiation. For this reason it seems advisable to divide the subject by discussing the more important species separately.

1. Alkaloids of *Veratrum Sabadilla* (*Cevadilla*).—The seeds of this species, also known as *Schænocaulon officinale* or *Asagrea officinalis*, have been the subject of considerable study. Following the discovery in 1819 by Meissner, and also by Pelletier and Caventou of an alkaloid in the cevadilla seeds, and the later work of Couerbe, Merck,² Weigelin,³ and Schmidt and Köppen,⁴ Wright and Luff⁵ made a rather exhaustive study of these seeds, and found three distinct alkaloids; an amorphous base, which they called veratrin, owing to its yielding veratric acid on saponification; a crystalline alkaloid, named cevadin, as it yielded cevadic acid on saponification; and an amorphous base, styled cevadillin, which was present in small amount and likewise yielded cevadic acid on saponification. In his studies Bosetti⁶ styled the crystalline base (the cevadin of Wright and Luff) veratrin, and the amorphous base (the veratrin of Wright and Luff) veratridin, a nomenclature adopted by Ahrens⁷ in recent work and also by Merck in his earlier investigations. In 1891 Merck⁸ isolated two new alkaloids, which he called sabadin and sabadinin.

While the above alkaloids are not found medicinally except as mixtures, yet the properties of these separate substances will be dis-

¹ See Prescott's Organic Analysis, 1887, p. 458.

² Ann. der Chem. u. Pharm., 1855, xcv, 200.

³ Dissert., Dorpat., 1871.

⁴ Ann. der Chem. u. Pharm., 1877, clxxxv, 224; Ber. d. d. Chem. Gesellsch., 1876, ix, 1115.

⁵ Jour. Chem. Soc., 1878, xxxiii, 338; Ibid., 1879, xxxv, 387.

⁶ Arch. der Pharm., 1883, ccxxi, 81.

⁷ Ber. d. d. chem. Gesellsch., 1890, xxiii, ii, 2700.

⁸ Chem. Zeit. Rep., 1891, xv, 48.

cussed briefly before speaking of the characteristics of the combined alkaloids, known officially as "veratrin."

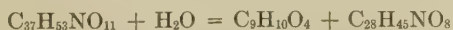
Cevadin ($C_{32}H_{49}NO_9$).—This alkaloid is identical with the crystalline "veratrin" of Merck and of Schmidt and Köppen, Bosetti, and Ahrens. It should not be confused with the "veratrin" of the pharmacopeias. On hydrolysis this base splits into an acid, cevadic acid (also known as methylcrotonic, angelic, or tiglic acid), and a new base, called cevin, according to the equation:



It is the most abundant of the alkaloids in *sabadilla* seeds, 10 kg. of these seeds yielding 12 to 15 grams of cevadin. Cevadin crystallizes from alcohol in rhombic prisms, which usually contain 2 molecules of alcohol of crystallization, or in anhydrous needles, while from ether it separates as a resinous mass, which becomes crystalline on adding slightly diluted alcohol with constant stirring. It dissolves easily in ether, hot alcohol, ethyl acetate, acetone, chloroform, amyl alcohol, and carbon disulphid, but is insoluble in water and only sparingly soluble in petroleic ether. Its solutions are optically inactive. When pure cevadin melts at 205° C. (401° F.).

Cevadin is a monacid, tertiary base, forming salts quite readily, but few of these have been obtained in the crystalline form. On adding a solution of gold chlorid to a solution of cevadin in hydrochloric acid, the gold salt is thrown down as a very sparingly soluble yellow precipitate, which is amorphous at first but soon becomes crystalline. If this gold salt be crystallized from alcohol it forms light yellow, glistening needles which melt with decomposition at 182° C. (359.6° F.). The picrate forms stable crystals, which are very slightly soluble in water, but readily in alcohol, and blacken when heated to 225° C. (437° F.). The mercurichlorid crystallizes in small silvery plates, which melt at 172° C. (341.6° F.) and are readily soluble in alcohol, but very slightly soluble in water. The platinichlorid is an amorphous precipitate, soluble in alcohol, but decomposed by water. On account of its weak basic properties, it may be extracted from its slightly acidulated solutions by the proper immiscible solvents.¹

Veratridin ($C_{37}H_{53}NO_{11}$).—This name was originated by Bosetti and applied to the amorphous base to which Wright and Luff gave the name "veratrin." As it yields veratric acid and verin on hydrolysis, the name veratrin might quite properly be applied to this alkaloid. It is probably identical with the amorphous alkaloid first isolated by Couerbe. Its saponification is shown by the equation:



Veratridin is soluble in water and forms crystallizable salts, although not itself crystallizable. The pure alkaloid melts at 180° C. (356° F.). On triturating solid veratridin with dilute nitric acid, a horny nitrate is

¹ See Barger, Allen's Commercial Organic Analysis, 1913, vii, 69; Schmidt, Abderhalden's Biochem. Handlexikon, 1911, v, 359.

formed, which is almost insoluble in water, even when boiling. Dilute sulphuric acid readily dissolves this alkaloid, the sulphate crystallizing out, on standing, as very slender needles. The hydrochlorid shows a similar property, but the crystals are not so well marked. The aurichlorid is obtained as a gelatinous yellow precipitate.

Cevadillin ($C_{34}H_{53}NO_8$).—This alkaloid of cevadilla seeds exists in small amount and is separated from cevadin by ether, which dissolves the latter and leaves the former undissolved. Like cevadin it yields cevadic acid, and probably also cevin on hydrolysis. It is a resinous material almost insoluble in ether, difficultly soluble in benzene, but easily soluble in amyl alcohol. Its salts are amorphous and gelatinous.

Sabadin ($C_{29}H_{51}NO_8$).—This base was found by Merck in sabadilla seeds. It is deposited by the slow evaporation of its alcoholic solution in well-defined needles, which melt, with decomposition, at 238° to 240° C. (460.4° to 464° F.). When freshly precipitated it is somewhat soluble in ether, but the crystallized base dissolves in ether with great difficulty. It is readily soluble in alcohol and acetone, but difficultly soluble in petroleic ether and in water. It forms crystallized hydrochlorid and nitrate, while its gold salt forms fine yellow needles, which are difficultly soluble in alcohol. On adding alkali hydroxids or carbonates or ammonia to cold solutions of its salts, sabadin is not precipitated, but is separated in a flocculent form on warming the liquid. It is easily extracted from the alkaline liquid by agitation with ether.

Sabadinin ($C_{27}H_{45}NO_8$).—This alkaloid was, likewise, first isolated by Merck. It separates from ethereal solution in hair-like needles, which commence to melt at 160° C. (320° F.), and decompose at a higher temperature. It is moderately soluble in water, readily soluble in alcohol, sparingly soluble in ether and petroleic ether. The hydrochlorid forms crystals with water of crystallization and which are readily soluble. The gold salt forms glittering yellow plates. The sulphate forms needles, which are difficultly soluble in water.

The Official "Veratrin."—This is a mixture of the alkaloids from the seed of *Asagraea officinalis*. It is a white or grayish-white amorphous powder, odorless, but causing intense irritation and sneezing when even a minute quantity reaches the nasal mucous membrane. It is slightly hygroscopic. Caution must be used in tasting it. One gram of veratrin dissolves in 1760 mils. of water, 2.8 mils. of alcohol, 0.7 mils. of chloroform, and in 4.2 mils. of ether at 25° C. (77° F.); also in 1345 mils. of water at 80° C. (176° F.); insoluble in petroleum benzin. Its alcoholic solution is alkaline to moistened litmus paper.

This veratrin is prone to be of variable quality and physiologic activity.¹ It contains, as its chief constituents, cevadin and veratridin, while cevadillin, sabadin, and sabadinin are present in small amount. The chief sternutatory element is cevadin, while sabadin and veratridin exert less marked effects. Cevadillin and sabadinin do not appear to cause sneezing. Even small quantities of the crystalline alkaloid (cevadin) render veratridin insoluble in water. On the

¹ See Pilcher, Jour. Pharm. and Exper. Therap., 1917, ix, 350.

other hand, veratridin will prevent cevadin from crystallizing. Hence, the crystallin base cannot be isolated by recrystallizing official veratrin from alcohol or from any other solvent; nor can the veratridin be obtained by simple extraction with water. On account of the variable composition of this official mixture of alkaloids of *sabadilla* seeds, the dosage is not stated.

2. The Alkaloids of *Veratrum Album*.—The rhizome of *Veratrum album*, white hellebore, was found by Pelletier and Caventou in 1820 to contain an alkaloid which they assumed to be identical with that obtained by them from *sabadilla* seeds and to which they gave the name veratrin. Since that time considerable work has been done on this plant, especially by Simon, Weigand, Weppen, Peugnet, Mitchell, Wormley, and Tobien. Wright and Luff,¹ in 1879, took up this investigation and announced that this root of white hellebore contained the crystallizable alkaloids, jervin, pseudojervin, rubijervin, an amorphous alkaloid called veratralbin, and a minute quantity of veratridin. Pehkschen² isolated the alkaloids veratroidin, jervin, and pseudojervin. The alkaloids of *veratrum album* were reinvestigated by Salzberger³ on very large amounts of material, his results representing the generally accepted ideas as to the alkaloids present in this root. He confirmed Wright and Luff's description of jervin, pseudojervin, and rubijervin, but doubted the existence of veratralbin. He isolated two new crystallizable alkaloids, protoveratrin and protoveratridin, and a small quantity of an unnamed crystallizable base. He pointed out that jervin has only a slight toxic action, and that pseudojervin is absolutely inactive, while he attributed the sternutatory property of *veratrum album* to protoveratrin, which is intensely poisonous.

Jervin ($C_{26}H_{37}NO_3$).—This is the principal crystalline alkaloid of *Veratrum album*, Wright and Luff reporting it present to the amount of 1.3 per cent. It crystallizes from alcohol in beautiful, satiny, prismatic needles, generally arranged in tufts, bundles, and stellar groups, showing a characteristic microscopic appearance. It melts according to different observers, from 237° to 242° C. (458.6° to 467.6° F.). It dissolves in methyl, ethyl, and amyl alcohols as well as in chloroform and acetone, while it is almost insoluble in water, ethyl acetate, benzene, and carbon disulphid, and completely insoluble in petroleic ether. It dissolves, when pure, in 268 parts of ether, but its solubility is greatly increased by the presence of amorphous alkaloids, and it is readily extracted by ether from alkaline aqueous liquids. The solutions of jervin are slightly levorotatory. It is a well-defined base, having an alkaline reaction to litmus and forms readily crystallizable salts with acids. It is easily precipitated by the general alkaloidal reagents, the precipitate with mercuric-potassium iodid being white, that with phosphomolybdic acid, phosphotungstic acid, cadmium-potassium iodid, and bromin water being yellow, that with iodo-potassium-iodid brown,

¹ Jour. Chem. Soc., 1879, xxxv, 405.

² Pharm. Seit. Russ., 1890, xxix, 339.

³ Arch. der Pharm., 1890, ccxxviii, 462. See Barger, loc. cit.

with picric acid yellow, and with gold and platinum chlorids clear orange red.

Pseudojervin ($C_{29}H_{43}NO_7$).—This alkaloid separates first as an amorphous mass, but when crystallized from alcohol forms thin, broad, hexagonal plates, which melt at $304^\circ C.$ ($597.2^\circ F.$). It is easily soluble in chloroform, difficultly soluble in alcohol and benzene, and almost insoluble in ethyl ether, petroleic ether, and toluol. Its alcoholic solution is alkaline toward litmus paper. It forms well-defined crystalline salts.

Rubijervin ($C_{26}H_{43}NO_2$).—This alkaloid crystallizes from hot alcohol in small prisms, melting at $234^\circ C.$ ($453.2^\circ F.$). It forms with acids easily crystallizable salts, which are quite easily soluble in water. The solutions of its salts are not precipitated by lead acetate, mercuric chlorid, platinum chlorid, or potassium chromate, but mercuric-potassium iodid, phosphomolybdic acid, phosphotungstic acid, and picric acid give yellowish white to yellow precipitates, iodo-potassium-iodid a brown deposit, and gold chlorid a reddish-yellow precipitate.

Veratralbin ($C_{32}H_{53}NO_9$).—This is the principal amorphous alkaloid of *Veratrum album*. It melts at about $149^\circ C.$ ($300.2^\circ F.$), and is optically inactive. It dissolves readily in alcohol and ether, chloroform, and benzene. The ordinary salts of this alkaloid are amorphous. It gives precipitates with most of the general alkaloidal reagents. According to Salzberger it is a decomposition product of protoveratrin or of other bases.

Protoveratrin ($C_{32}H_{51}NO_{11}$).—This base represents the active, poisonous principal of white hellebore. It crystallizes from dilute solutions in microscopic, quadrilateral plates, which melt with charring at 245° to $250^\circ C.$ (473° to $482^\circ F.$). It is somewhat soluble in chloroform and hot alcohol, very slightly soluble in cold ether, somewhat more soluble in boiling ether, insoluble in water, benzene, and petroleic ether. It is soluble in dilute acids with the exception of acetic acid. Solutions of salts of protoveratrin are precipitated by ammonia, Nessler's solution, Mayer's reagent, potassio-cadmium iodid, phosphotungstic acid, and picric acid; but not by tannic acid, platinic chlorid, or mercuric chlorid. Gold chlorid throws down a golden-yellow amorphous precipitate. It is probable that this alkaloid can be hydrolyzed, although exact results along this line do not seem to have been reported. In this respect it differs from the other alkaloids of *veratrum album*, as these seem to be unaffected by prolonged boiling with alcoholic potassium hydroxid. Although this is the essential active principal of white hellebore it is present in small amount, Salzberger obtaining only 0.03 per cent. from this root.

Protoveratridin ($C_{26}H_{45}NO_8$).—This appears to be a decomposition product of protoveratrin, and is not present as such in the root of white hellebore. It crystallizes in colorless, four-sided plates, melting at $265^\circ C.$ ($509^\circ F.$). It is almost insoluble in alcohol, methyl alcohol, acetone, or chloroform, and quite insoluble in ether, benzene, and petroleic ether. Its solutions in acids are very bitter and form crystalline precipitates with ammonia. Solutions of its salts yield copious precipitates with

phosphotungstic, tannic, and picric acids, and with Mayer's reagent. The platinum chlorid salt is formed as a precipitate of large hexagonal plates on adding alcohol to mixed solutions of platinic chlorid and protoveratridin hydrochlorid.

3. The Alkaloids of *Veratrum Viride*.—The dried rhizome and roots of *Veratrum viride* are official in the United States. The rhizome is upright, obconical, usually cut longitudinally into two to four pieces, from 2 to 7 cm. in length, and from 1.5 to 3 cm. in diameter, externally light brown to dark brown or brownish black, frequently bearing at the summit numerous closely arranged, thin leaf-bases, otherwise rough and wrinkled, somewhat annulate from scars of bud-scales and bearing in the outer portion numerous roots, the lower part more or less decayed; fracture hard and horny; internally yellowish or grayish white, marked with numerous, irregular fibrovascular bundles; inodorous but sternutatory; taste bitter and acrid. The roots are nearly cylindrical, from 3 to 8 cm. in length, and from 1 to 3 mm. in diameter, externally light brown to yellowish brown, deeply transversely wrinkled; fracture short, bark whitish, very thick, enclosing a porous central cylinder. Official preparations of veratrum viride are the fluidextract and the tincture.

This green or American hellebore is commonly known as "Indian Poke" (the name "poke" being generally applied to *Phytolacca decandra*). It contains essentially the same alkaloids as does veratrum album. A mass of conflicting reports as to the constitution of green hellebore appears in the literature, the work of Worthington, Richardson, Scattergood, Percy, Bullock, Wood, Peugnet, Mitchell, and Wormley giving us no settled idea of the alkaloids present. Wright and Luff,¹ using improved methods, found the same five alkaloids which they had isolated from white hellebore, and in addition a certain amount of cevadin, which was noted in *sabadilla* but not in white hellebore. No examinations have been made along the lines of Salzberger's investigations, so that the presence or absence of protoveratrin and protoveratridin is still undetermined.

Symptoms of Poisoning by *Veratrum Alkaloids*.—As previously shown the poisonous principles of the various species of veratrum are cevadin and protoveratrin. The symptoms of poisoning usually appear within a few (twenty) minutes, but may be delayed for an hour or more. These are referable both to the action of the alkaloids on the terminations of the motor, sensory, and secretory nerves and to the action on the central nervous system, both of which actions resemble, to a certain extent, those noted following aconitin poisoning.

The symptoms begin with prickling and burning in the mouth followed by a sensation of warmth and intense burning pain in the stomach. There is great thirst, and the patient has difficulty in swallowing. Then follow salivation; marked nausea with severe and persistent vomiting; violent purging accompanied by tenesmus and severe abdominal colic are common. The prickling sensations soon spread from

¹ Jour. Chem. Soc., 1879, xxv, 421.

the mouth and throat to the skin which becomes reddened and is affected with an intense itching, generally followed by a profuse perspiration. Sneezing, lachrimation, and coryza may occur but are not constant. Patient is restless and becomes gradually prostrated; extremities are cold; vertigo may appear; pupil is dilated and almost complete lack of vision may be noted. The respiration becomes gasping, shallow, and superficial, while severe dyspneic attacks are not uncommon. Pulse is first slow and irregular due to the vagus stimulation, but later, owing to paralysis of the vagus, becomes feeble, small, thready, and rapid with a coincident lowering of blood-pressure due to vasomotor paralysis.¹ Death is usually due to respiratory failure, although it may occur from collapse due to cardiac weakness or to exhaustion from long-continued vomiting and consequent prostration. Death occurs sometimes in five or six hours, but more often after twenty-four hours or longer.

The **fatal quantity** of the drug cannot be safely declared, on account of great differences in susceptibility to this agent. The medicinal dose of the fluidextract is from 1 to 3 minims (0.06–0.18 c.c.), and of the tincture, 8 minims, results to be closely watched and administration suspended if there is nausea (see notes of cases of poisoning below).

Treatment of Poisoning by Hellebore.—The stomach should be well washed out with warm water. The patient should then be kept strictly upon his back, with the head lower than the feet, and vomiting should be restrained. Warm applications, especially to the feet, and external stimuli should be kept up. A dose of tincture of opium may be administered by the rectum, undiluted spirits by the mouth, and ammonia at discretion. To meet failure of respiration Böhm and Lis-sauer (1887) propose atropin hypodermically, but strychnin and digitalis are more directly indicated.

CASES OF POISONING BY VERATRUM VIRIDE

CASE 1.—A man took 1 dram (3.7 c.c.) of tincture, equal to 12 grains (0.77 gm.) of the powder. The symptoms consisted of collapse, cold and perspiring skin, scarcely perceptible pulse, pain in the stomach, but no purging. Result, recovery.²

CASE 2.—A child of eighteen months took four or five doses of 4 minims (0.24 c.c.) each, and then one dose of 16 minims (1 c.c.) of the tincture. There occurred attempts at vomiting, unconsciousness, and stertorous breathing beginning eight hours after the first dose; the pulse was slow, the skin in cold perspiration. Result, death in thirteen hours.³

CASE 3.—A woman of fifty years took 70 minims (4.3 c.c.) of a fluidextract of veratrum viride in two doses. Pain in the stomach, nausea, and vomiting occurred in two hours after the first dose. In two hours after the second dose the symptoms became more severe and there was great prostration. After twelve hours the stools were bloody. Vomiting continued for four weeks, when the patient died.⁴

CASE 4.—An adult male took a teaspoonful of the fluidextract of veratrum viride. In thirty minutes he became speechless, with violent vomiting, the pulse being almost imperceptible, and the skin bathed in cold perspiration. The patient recovered.⁵

¹ The results of Pilcher and Sollmann (*Jour. Pharm. and Exp. Therap.*, 1915, vii, 295) indicate that veratrum alkaloids are without effect on the vasomotor center.

² Edwards, *Med. Times and Gaz.*, 1863, i, 5.

³ J. C. Harris, *Boston Med. and Surg. Jour.*, 1865, lxxii, 249.

⁴ T. M. Johnson, *Buffalo Med. and Surg. Jour.*, 1866, vi, 133.

⁵ J. B. Buckingham, *Amer. Jour. Med. Sci.*, 1865, n. s., i, 563. For other cases see Clerc, *Dauphine méd.*, 1911, xxxv, 117; Martin, *Arch. d'anthrop. crim.*, 1913, xxviii, 199.

Postmortem Appearances.—These are neither distinctive nor uniform, but usually include signs of congestion of the lining of the stomach and bowels and sometimes hyperemia of the brain and its membranes. The kidneys should be examined.

Chemical Tests for Veratrum Alkaloids.—In the usual course of a toxicologic analysis it is probable that a mixture of alkaloids would be obtained in a case of veratrum poisoning, as the veratrum alkaloids are difficultly separable. For this reason the tests usually employed for differentiating the mixed alkaloids of veratrum from other alkaloids will be given, and reference made to the variation shown by the separate alkaloids.

1. **Concentrated Sulphuric Acid Test.**—If a few drops of concentrated sulphuric acid be poured upon a portion of official veratrin or upon the residue of mixed alkaloids obtained in the extraction processes, the alkaloid will assume an intense yellow color and will dissolve to a yellow solution. This soon changes to an orange shade with a strong greenish fluorescence shown by reflected light. This fluorescence may not be noted unless the alkaloid be present in quite appreciable amount. On standing the orange solution gradually changes to a red and then to a deep carmine-red color, which persists for some hours. Gentle heating of veratrin with strong sulphuric acid produces a cherry-red color almost immediately, the persistence of this red color being very characteristic of the veratrum alkaloids. Erdmann's, Fröhde's, and Mandelin's reagents give the same results as does sulphuric acid itself. Likewise, the addition of bromin water to the yellow solution above will give a purple color, as shown by Grandeau. The above reaction is given by cevadin, while veratridin and sabadillin do not show the greenish fluorescence, and sabadin gives a yellow solution with green fluorescence, the color later changing to blood red and finally to violet. The separate alkaloids of *Veratrum album* and *viride* show the following changes when treated with concentrated sulphuric acid; jervin gives a yellow, brownish-yellow, and then a bright green; rubijervin strikes a yellow, then orange, and finally dark red; veratralbin reacts exactly as does the official veratrin; pseudojervin gives a yellow then a bright green; protoveratrin shows a greenish blue, and finally a violet; while protoveratridin strikes a violet changing to cherry red. Various organic compounds give red colors with sulphuric acid, but comparative tests made with known veratrin and sulphuric acid as well as other tests to be mentioned will differentiate the veratrum alkaloids.

2. **Concentrated Hydrochloric Acid Test.**—Strong hydrochloric acid dissolves veratrin without change of color, but upon boiling this solution a bright-red color is developed, which persists for days or even weeks. This test is quite characteristic, although it is not extremely delicate as it requires about 0.1 mg. of the mixed alkaloids for reliable results. Cevadin gives this same reaction; jervin shows no color; veratralbin gives a rose color; protoveratrin and protoveratridin give a cherry-red color, and an odor of isobutyric acid.

3. Concentrated Nitric Acid Test.—Veratrin dissolves in concentrated nitric acid with a yellow color. Cevadin reacts as does veratrin, while sabadin and sabadillin show no coloration. Jervin shows an initial pink changing to colorless; veratralbin strikes a rose color quickly changing to pale yellow.

4. Weppen's Test.—If 1 part of veratrin be thoroughly mixed with 6 parts of finely powdered cane-sugar and treated with concentrated sulphuric acid, a yellow color will appear which changes to grass green and then to blue, the mixture finally becoming colorless. This test is quite characteristic of the veratrum alkaloids. Cevadin shows the above reaction, while jervin gives a yellow, brown, and then dark brown; protoveratrin a green, olive green, then dark brown, and veratralbin a brown color.

5. Laves' Test.—Laves has modified the above test as follows: To 1 c.c. of pure concentrated sulphuric acid in a test-tube add 3 or 4 drops of a 1 per cent. aqueous solution of furfural and mix. Add 3 to 5 drops of this solution to the residue to be tested, so that it just touches the edge of the liquid. If veratrum alkaloids are present, a dark streak will gradually run from the substance into the liquid. At the starting-point it will appear blue or blue violet and farther away green. If the substance and liquid are stirred with a glass rod, the liquid will become dark green, and after some time blue and finally violet.

6. Vitali's Test.—Dissolve the suspected residue in a few drops of fuming nitric acid and evaporate the solution to dryness upon the water-bath. A yellowish residue will remain. If this be cooled and then treated with a few drops of an alcoholic potassium hydroxid solution, the color will change to reddish violet. This test is not characteristic for the veratrum alkaloids as it is given by the atropin group of alkaloids as well as by strychnin in a very similar manner.

Biologic Test for the Veratrum Alkaloids.—If a small quantity of a very slightly acid solution of the suspected residue be injected into the lymph-sac of a frog, there occur movements as if the animal were going to vomit, the heart's action is immediately slowed, and a curious clumsiness and awkwardness in the movements becomes apparent, which shortly indicate spasmodic contractions of the muscles and an inability to relax them. The animal loses its power of co-ordination.

Separation from the Tissues or Contents of the Stomach.—It must be borne in mind that chloroform, benzene, and amyl alcohol respectively dissolve veratrum alkaloids, to some extent, from *acidulous*, as well as from alkaline, water solutions. Chloroform is, in general, the best solvent, applying it to feebly alkaline solutions. The process given under Atropin may be employed, omitting the chloroformic washing of the acidulous solution, and continuing the steps of purification until a sufficiently colorless residue is obtained.

The kidneys and the urine should be subjected to analysis, as this poison is eliminated to some extent by the kidneys.

Veratrin-like Ptomaines.—Ptomaines have been found closely

resembling veratrin under the color-tests, but not at all responding to the physiologic test. Thus Brouardel and Boutmy¹ obtained from a corpse that had lain in water for eighteen months, and a large part of which had changed to adipocere, a substance that resembled veratrin. It was extracted from alkaline solutions with ether. On being heated with sulphuric acid it became violet; with a mixture of sulphuric acid and barium peroxid it became dark red in the cold, and violet on being heated. On being boiled with hydrochloric acid it took on a cherry-red coloration. It differed from veratrin inasmuch as it reduced ferric salts immediately. When injected into frogs subcutaneously, it did not produce the spasmodic muscular contractions shown by veratrin. By the Stas-Otto method Bechamp² obtained from the products of the pancreatic digestion of fibrin a basic substance that gave with sulphuric acid a beautiful carmine-red color similar to that given by veratrin. By digesting this substance with gastric juice and again extracting, he obtained a body that behaved with sulphuric acid similar to curarin, that is, it was colored red. Stuber³ obtained from the cadavers of rats which died in the hold of an infected ship, whose cargo contained cotton-seed oil and maize, a yellowish, amorphous substance which was colored yellowish brown with sulphuric acid, changing to orange and violet; and with hydrochloric acid when heated gave a fine cherry-red color. It did not respond to Weppen's reaction nor did it give the biologic test.

¹ *Moniteur scient.*, 1878, 3 s., x, 1140.

² *Ber. d. d. chem. Ges.*, 1882, xv, 1584.

³ *Ztschr. f. Unt. d. Nahr. u. Gen. Mitt.*, 1903, vi, 1137.

NON-ALKALOIDAL ORGANIC POISONS

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PETROLEUM PRODUCTS

MIXTURES of paraffin hydrocarbons which boil below 150° C. (302° F.) are known as benzin, gasolin, petroleum naphtha, etc.; they consist chiefly of pentane, hexane, and heptane, and, in the case of the higher boiling fractions, also octane.

These mixtures are poisonous when inhaled in the form of their vapors or when taken by mouth; poisoning of the former type is usually industrial or accidental, that of the latter (most frequent in children) accidental; occasionally they have been taken with suicidal intent. Ten fatal cases were reported in the registration area of the United States for 1909.

Applied locally they are irritants of mucous membranes; after absorption their effects are in general similar to those of the alcohol-ether group of anesthetics and the more volatile of them have been used to a limited extent in anesthetic mixtures; in animals¹ they cause excitement, convulsions, unconsciousness, and death from failure of respiration; their anesthetic action from a practical standpoint is weak.² Administered to man by inhalation³ they cause dizziness, nausea, vomiting, a burning sensation in the chest, drowsiness, and sleep; 2 to 2.5 per cent. of the vapor renders a man dizzy and soon becomes intolerable.

Acute poisoning by inhalation has frequently occurred in men engaged in cleaning gasolin tanks and among those engaged in industries in which these products are used as solvents (in the rubber industry,⁴ for example) and among painters,⁵ dry-cleaners, etc. An infant⁶ from whom plasters were removed with the aid of benzin was poisoned; also a woman who washed her hair with gasolin in a small bath room.⁷ Cases of poisoning have been reported in engineers and chauffeurs operating engines in tunnels or closed garages; in these cases, however, carbon monoxid was doubtless the chief toxic agent.

In cases of mild poisoning the symptoms are suggestive of those of mild alcohol intoxication ("naphtha jag"), lack of self-control being a

¹ Sollmann, *Amer. Jour. Med. Sci.*, 1904, 128, 427; Haggard, *Jour. Pharm. exp. Therap.*, 1920, 16, 401; Fühner, *Bioch. Zeitsch.*, 1921, 115, 235.

² Kochmann, *Arch. int. Pharmac. et Thér.*, 1903, 10, 347.

³ Compare Lehmann, *Arch. f. Hygiene*, 1911, 74, 1.

⁴ Hamilton, *Bureau of Labor Statistics No.* 179, 1918.

⁵ Harris, *Arch. Int. Med.*, 1918, 22, 129.

⁶ Friedberger, *Münch. med. Woch.*, 1912, 59, 252.

⁷ Houghton, *Brit. Med. Jour.*, 1908, ii, 1747.

prominent symptom. These effects are followed by depression, headache, nausea, heaviness, roaring in the ears, feeling of irritation and constriction in the throat, trembling of the hands and arms, and staggering. In more severe cases¹ the patients become very pale, the lips are livid, the respiration slow, the heart's action weak and scarcely perceptible; insensibility, frequently convulsions, and sometimes death occur.

Cases of chronic poisoning have been reported²: the symptoms were abdominal pain, nausea, vomiting; weakness and heaviness of the arms and legs; paresthesias, dizziness, and drowsiness. Recovery occurred when the subjects were removed from the contaminated atmosphere.

The symptoms from the ingestion of benzin, which consist in dyspnea, cyanosis, unconsciousness, coldness of the skin, and dilatation of the pupils,³ are especially severe in children; of 9 fatal cases collected by Jaffé, 8 occurred in children. Ten to 15 grams ($\frac{1}{3}$ to $\frac{1}{2}$ oz.) have proved fatal, death usually occurring in from ten minutes to four hours. A girl of twenty died in five hours from 30 grams (1 oz.); another recovered from 250 c.c. The postmortem findings have sometimes been practically negative⁴; in other cases, hyperemia and small hemorrhages in the gastro-intestinal tract and slight changes in the kidneys⁵; also hemorrhages into the lungs⁶ and some hemolysis⁷ have been described. The gastric contents have the odor of the oil.

Skin eruptions attributed to benzin have been reported from the wearing of gloves recently cleaned with benzin, and from the use of benzin in cleaning type, etc.; impurities or adulterants may have been a factor in some of these cases.⁸

Poisoning by **kerosene**, or "coal oil" (the fraction of petroleum distilling between 150° C. (302° F.) and about 300° C. (572° F.), is not uncommon, especially in children, but fatal cases are very rare. The most marked symptoms⁹ result from the local action upon the gastro-intestinal tract and consist in a burning pain in the throat and stomach, vomiting, colicky pains, diarrhea, great thirst, painful micturition, etc.; drowsiness, cyanosis, labored respiration, and unconsciousness may follow.¹⁰ The fatal dose is unknown: as much as a liter has been taken without causing death, but children have died after taking small, but unknown amounts.

¹ Foulerton, *Lancet*, 1886, ii, 865; Burgi, *Korrespondenzbl. f. Schw. Aerzte*, 1906, 36, 11; Wichern, *Münch. med. Woch.*, 1909, 56, 11.

² Dorendorff, *Münch. med. Woch.*, 1901, 48, 236. Hamilton, loc. cit.; Haden, *Johns Hopkins Hosp. Bull.*, 1919, 30, 309.

³ Böhme and Köster, *Arch. exp. Path. u. Pharm.*, 1917, 81, 1; Jaffé, *Münch. med. Woch.*, 1914, 61, 175.

⁴ Rosenthal, *Zentralbl. f. inn. Med.*, 1894, p. 281.

⁵ Böhme and Köster, loc. cit.

⁶ Compare Jaffé, loc. cit.; Zörnlaib, *Wien. med. Woch.*, 1906, 56, 366.

⁷ Burgi, *Münch. med. Woch.*, 1906, 53, 412; see, however, Jaffé, loc. cit.; Böhme and Köster, loc. cit.

⁸ Zellner and Wolff, *Zeitsch. f. Hyg.*, 1913, 75, 69.

⁹ Vincent, *Brit. Med. Jour.*, 1886, i, 543; Friedberg, *Centrbl. f. inn. Med.*, 1902, 1041.

¹⁰ Johannessen, *Berl. klin. Woch.*, 1896, 33, pp. 317, 349.

Liquid petrolatum (Petrolatum Liquidum, U. S. P.; "liquid paraffin," "mineral oil," etc.) consists chiefly of naphthenes; it is widely used as a laxative, and the lighter forms for sprays. Its ingestion is occasionally followed by nausea and regurgitation; none, or at most only traces, are absorbed and there are no systemic effects.

Liquid petrolatum has been extensively used as a solvent for camphor and as a means of holding insoluble mercury preparations in suspension for subcutaneous or intramuscular injection, and also as an ingredient of the "bismuth and iodoform paste." In a number of cases¹ tumors have formed in from two weeks to sixteen years² after such use; these tumors, which are fibromata or granulomata, may become inflamed and tender. Similar tumors (paraffinomata) may result from the subcutaneous injection of paraffin for cosmetic purposes³; there is also danger of embolism, and amaurosis has been reported a number of times.

Petrolatum (U. S. P.) ("vaselin," petroleum jelly), a mixture of semi-solid hydrocarbons obtained from petroleum has caused some irritation of the stomach when taken internally as for the treatment of colds.⁴

Men engaged in various phases of the petroleum⁵ and paraffin⁶ industries, and in industries in which those products are used,⁷ suffer from a variety of skin lesions⁸; these are due in part to the irritant action of the products themselves or to that of impurities, and in part to infection (oil folliculitis⁹).

The **treatment** of poisoning by these products consists in removing the patient from the contaminated atmosphere if the poison has been inhaled, and the removal of clothing if this has been in contact with the liquid; warm baths with cold affusions or artificial respiration may be needed. If the poison has been swallowed the stomach should, in addition, be washed out.

Detection.—The constituents of petroleum may be shown in the tissues by fractional distillation, the various fractions being recognized by their odor, boiling-point, inflammability, and other properties.

METHYL ALCOHOL

Methyl alcohol (methanol, methylic or wood alcohol, pyroligneous or wood spirit, CH_3OH) is obtained by the destructive distillation of wood. It occurs in commerce in varying degrees of purity. The crude wood alcohol contains much acetone, some ethyl-methyl-ketone,

¹ Jacob, Bull. Soc. Biol., 1917, 80, 371; Jacob and Fauré-Fremont, Rev. de Chir., 1917, 36, 221; Mook and Wander, Arch. Dermatol. and Syphilol., 1920, 1, 304; Stokes and Scholl, Ibid., 1921, 4, 50.

² Algave, Bull. et mem. Soc. de Chir. de Par., 1920, 46, 649.

³ Heidensfeld, Jour. Amer. Med. Assoc., 1908, 51, 2028; Davis, Ibid., 1920, 75, 1709.

⁴ Robinson, Brit. Med. Jour., 1886, i, 296.

⁵ Lewin, Virchow's Arch., 1888, 112, pp. 35, 59.

⁶ Davis, Jour. Amer. Med. Assoc., 1914, 62, 1716.

⁷ Compare Suppl. Jour. Ind. Hyg., 1919-20, 1, pp. 22, 174; 1921, 2, 215.

⁸ Schamberg, Jour. Cutan. Diseases, 1910, 28, 644; Bettmann, Münch. med. Woch., 1918, 45, 1344.

⁹ Page and Bushnell, Jour. Ind. Hyg., 1921, 3, 67.

methyl and dimethyl acetate, furfural, allyl alcohol, and other bodies that give it an extremely disagreeable odor and taste; it is used as a denaturing agent for grain alcohol. Purified methyl alcohol is now extensively used under the names of "Columbian spirits," "Colonial spirits," "Eagle spirits," etc.

Pure methyl alcohol is a colorless liquid with a specific gravity of 0.8021 at 15.5° C. (59.5° F.). It boils at 66° C. (150° F.), and has a pungent taste and an odor not very different from that of ethyl alcohol. On oxidation it yields formaldehyd and then formic acid. Methyl alcohol is used very extensively in the arts as a substitute for ethyl or grain alcohol as a solvent, especially of varnishes; it has also been used, with most disastrous results to those taking the preparations, as a solvent in the preparation of essences of Jamaica ginger, peppermint, etc., and of spirits of cologne and bay rum, and as an adulterant of whisky and other beverages.

Prior to 1898 only 3 or 4 cases of poisoning were reported from methyl alcohol; in that year MacCoy and Michael¹ reported a case of blindness from drinking Columbian spirits. At about the same time cases of blindness began to be reported from the drinking of essence of Jamaica ginger²; these were first attributed to the ginger, as the manufacturers denied having used methyl alcohol in the preparation. Many other cases were soon reported from the use of methyl alcohol itself, and from the drinking of preparations (essence of peppermint, cinnamon, vanilla, lemon, bay rum, eau-de-cologne, "Florida water," witch hazel, adulterated sherry, rum, whisky, cider, "bitters," "liniments," etc.) containing methyl alcohol; many of these cases were reported from "prohibition" districts of Maryland, Virginia, Maine, the Indian Territory, etc.

Cases of blindness from the inhalation³ of the vapors of methyl alcohol (from the shellacking of beer vats, closets, floors, furniture, etc.) were also early reported.

In 1904 Buller and Wood⁴ collected 275 cases of serious poisoning by methyl alcohol; in 153 blindness, in 122 death, occurred. Many cases of wholesale poisoning have occurred both in the United States and abroad⁵; in Berlin⁶ about 130 men drank "brandy" composed of two-thirds methyl alcohol and one-third ethyl alcohol, 50 or more died, 42 became blind or had impairment of vision, and 32 recovered.

Baskerville⁷ collected 725 published cases of poisoning resulting from the drinking of wood alcohol: there were 390 deaths, 90 cases of total

¹ MacCoy and Michael, *Med. Rec.*, 1898, 53, 777.

² Thompson, *Proc. Phila. Med. Soc.*, 1897; also *Med. and Surg. Rep.*, 1897, 77, 97; Woods, *Ophthalmic Record*, 1899, 8, 55.

³ Patillo, *Ophth. Rec.*, 1899, 8, 599; de Schweinitz, *Ibid.*, 1901, 10, 289; Hale, *Jour. Amer. Med. Assoc.*, 1901, 37, 1450; Ziegler, *Jour. Amer. Med. Assoc.*, 1921, 77, 1160.

⁴ Buller and Wood, *Jour. Amer. Med. Assoc.*, 1904, 43, 972, 1058, 1117, 1213, 1289.

⁵ Compare Ströhmberg, *Petersb. med. Woch.*, 1904, 31, 55 (51 deaths).

⁶ Compare Stadelmann and Magnus-Levy, *Berl. klin. Woch.*, 1912, 49, 193.

⁷ 2d Rep., *Factory Inves. Com.*, New York, 1913, 2, 921.

blindness, 85 of impaired vision; in about 100 cases the results were not specifically stated.

Baskerville also collected 64 cases of poisoning by the inhalation of methyl alcohol.¹ Blindness has resulted from the external use of methyl alcohol.²

The above figures, however, give but an imperfect picture of the extent of methyl alcohol poisoning.

Apparently all of the cases so far reported have been due to accident or to the use of the alcohol as an adulterant or as a beverage.

Action.³—Although it had long been known to pharmacologists that in some respects the action of methyl alcohol is so fundamentally different from that of ethyl, or grain, alcohol that the substitution of the former for the latter in any preparation intended for internal use (especially if the preparation were to be taken for some time) would inevitably be accompanied by the greatest danger, this was ignored by chemists and manufacturers until recently. The effects upon animals of a single dose of methyl alcohol do not differ markedly from those of a corresponding amount of ethyl alcohol: the symptoms may, however, appear more slowly and the duration of the intoxication be more prolonged; the condition of coma caused by methyl alcohol may continue for two, three, or even four days, whereas that caused by ethyl alcohol may not continue for more than six hours, and in numerous experiments never continued for twenty-four hours. It also requires as much, or a little more, ethyl alcohol to cause acute death in animals as of methyl alcohol; after equal doses of the two alcohols, death occurs more quickly after ethyl than after methyl alcohol. Thus in acute fatal intoxication of the lower animals, methyl alcohol is slightly less toxic than ethyl alcohol.⁴ This probably does not hold for man, however; for methyl alcohol, even in the lower animals, affects most powerfully the most highly differentiated nervous structures, as is shown by the prolonged coma, and it is a well recognized fact in pharmacology that poisons which affect the highly differentiated nerve structures very powerfully are proportionately more dangerous the more highly developed the nervous system of the animal.

The cause of the more prolonged action of methyl than of ethyl alcohol is to be sought in the difference in the fate of the two in the body; ethyl alcohol is easily and comparatively quickly oxidized to carbon dioxid and water, which are quickly excreted. On the other hand, the body has great difficulty in disposing of methyl alcohol; some is slowly excreted in the urine, and in the expired air⁵; Asser⁶ recovered from the latter in seven days, 55.8 per cent. of 25 c.c. given to a dog. Some is

¹ Compare also Wood, Jour. Amer. Med. Assoc., 1912, 59, 1962 (Case 2).

² Compare Woods, *Ibid.*, 1913, 60, 1762.

³ See Pohl, Arch. f. exper. Path. u. Pharmacol., 1892-93, 31, 281; Hunt, Johns Hopkins Hospital Bull., 1902, 13, 213; Langgard, Zeit. f. exp. Path. u. Ther., 1913, 13, 20; Sollmann, Jour. Pharmacol. and exp. Therap., 1920, 16, 291.

⁴ Hunt, *Loc. cit.*; Nicloux and Placet, Jour. de physiol. et path., 1912, 14, 916.

⁵ Völtz and Dietrich, Bioch. Zeit., 1912, 40, 15.

⁶ Zeitz. f. exp. Path. u. Ther., 1914, 15, 322.

excreted into the stomach,¹ and is doubtless reabsorbed from this organ or from the intestines. The body oxidizes methyl alcohol slowly and incompletely with the formation of formic acid²; in one of Pohl's experiments 60 c.c. of methyl alcohol were given to a dog and the maximum amount of formic acid did not appear in the urine until the fourth day, and there was an abnormal amount present three days later. There is a profound disturbance of metabolism; a condition of acidosis develops,³ and there is also a marked increase in the excretion of lactic and other organic acids.

This prolonged retention in the body of methyl alcohol, and the products of its oxidation, sufficiently explain the marked differences between the effects of pure ethyl and pure methyl alcohol, when given in small repeated doses: a tolerance is established for the former, but the latter has a marked cumulative action.

Symptoms.⁴—The symptoms are for the most part unlike those of ethyl alcohol poisoning; a condition of exaltation such as is seen in the latter seems to have rarely occurred in methyl alcohol poisoning. There is depression, weakness, and headache; nausea, excruciating pains in the epigastric and temporal regions; dyspnea and cyanosis; delirium or a maniacal condition, or stupor from which the patient is aroused by pain and vomiting; cold sweats and subnormal temperature; dilated pupils not reacting to light; there may be long continued coma and death from failure of the respiration, but in other cases consciousness has been preserved almost until death; convulsions may precede the latter. A condition of coma may continue for three or four days, and recovery, except for blindness, occur.⁵ Barbash⁶ reports thrombosis of the radial artery with resulting gangrene of the hand as a complication of one of his cases.

Even in cases which end fatally distinct symptoms may not appear for twenty-four to thirty-six hours, and the victims may continue their work. Cases may seem to be recovering, and sudden relapse and death occur.

The symptom which has aroused most interest is blindness, which was early reported by a number of American ophthalmologists.⁷ Blindness has occurred in a large percentage of severe cases of poisoning; it is bilateral, and may set in in a few hours or it may be delayed for several days. There is first usually a feeling of pain about the eyes, and tender-

¹ Bongers, Arch. exp. Path. u. Pharmacol., 1895, 35, 415.

² Pohl, Arch. f. exp. Path. u. Pharmacol., 1892-93, 31, 281; Rabinovitch, Arch. Int. Med., 1922, 29, 821.

³ Krol, Ibid., 1913, 72, 444; Harrop and Benedict, Jour. Amer. Med. Assoc., 1920, 74, 25; Van Slyke and Palmer, Jour. Biol. Chem., 1920, 41, 567.

⁴ Buller and Wood, Jour. Am. Med. Assoc., 1904, 43, 972, 1058, 1117, 1213, 1289; Stadelmann and Magnus-Levy, Berl. klin. Woch., 1912, 49, 193; Ströhmberg, Petersb. Med. Woch., 1904, 31, 55; Wood, New York Med. Jour., 1905, 81, 5; Pierce, Boston Med. and Surg. Jour., 1909, 160, 232.

⁵ Moulton, Jour. Amer. Med. Assoc., 1901, 37, 1447; Swadener, Ibid., 1913, 60, 1479.

⁶ Jour. Amer. Med. Assoc., 1922, 78, 430.

⁷ Thompson, Med. and Surg. Rep., 1897, 77, 97; Woods, Loc. cit.; Harlan, Ophthal. Rec., 1901, 10, 81; Wurdemann, Amer. Med., 1901, 2, 995; Moulton, Ther. Gaz., 1899, 8, 335; Burnett, Ibid., 1901, 10, 801; Buller and Wood, Loc. cit.; Friedenwald, Ophthal. Rec., 1901, 10, 429; Wood, New York Med. Jour., 1905, 81, 5, and many others.

ness on pressure over the lids, discomfort on looking about, slight photophobia and dilatation of the pupil. The subsequent history has been very uniform (Case 1).

The vision became blurred, and in from twelve to forty-eight hours the patient became totally blind; after a few days, there was a gradual return of sight—to some useful vision, only to be lost again in a short time or within a few weeks. The blindness is due to atrophy of the optic nerve.¹ In nearly every case a central scotoma was demonstrated. In some cases some peripheral vision was preserved, but the field was always narrowed. Sometimes the color sense was chiefly affected.²

In some cases of methyl-alcohol poisoning practically the only symptom has been the blindness. Thus Gifford³ reported a case in which a man became temporarily blind in three days from drinking cologne spirits made with methyl alcohol; so slight were the other symptoms that the patient had forgotten that he had drank the cologne. In other cases in which a large quantity of the poison had been taken the patients were comatose for two or three days, and then awoke almost blind.⁴

The **diagnosis** is based upon the above symptoms and the presence of abnormally large amounts of formic acid in the urine.⁵

Fatal Dose.—Individuals differ greatly in their susceptibility to the poison. Thirty to 60 c.c. (1 or 2 oz.) seem to have been fatal.⁶ Swadener reported a case in which each of 4 Indians drank 4 ounces of methyl alcohol: 2 died on the third and fourth day; 1 was comatose for three days and recovered, blind; the fourth showed few symptoms. Death has been reported from 90 and 150 c.c. (3 and 5 oz.)⁷; 180 and 240 c.c. (6 and 8 oz.) have repeatedly caused death, but recovery has followed larger amounts.

Moulton⁸ mentions an instance in which 5 men drank about $\frac{1}{2}$ pint of wood alcohol each; all became very ill; 2 died within twenty-four hours, 2 recovered entirely, while the fifth recovered, but with complete atrophy of the optic nerve of the right eye and great contraction of the field of vision of the left eye.

Blindness or serious impairment of vision has been reported from 15 c.c. ($\frac{1}{2}$ oz.),⁹ 20 to 23 c.c. ($\frac{2}{3}$ to $\frac{3}{4}$ oz.),¹⁰ and 60 c.c. (2 oz.); much larger amounts have been taken without either temporary or permanent injury to the eyes.

Buller and Wood concluded that if 10 persons drank, say, 4 ounces

¹ See Friedenwald, *Ophthal. Rec.*, 1901, x, 429, and Birch-Hirschfeld, von Graefe's *Arch. f. Ophthal.*, 1902, liv, 68; Uhthoff, *Graefe-Saemisch Handbuch*, 2d ed., 1907, v, 11.

² Burnett, *Ophthalmic Record*, 1902, xi, 309.

³ *Ibid.*, 1901, x, 342.

⁴ Harlan, *Ibid.*, 1901, x, 81.

⁵ Autenrieth, *Munch. med. Woch.*, 1919, 66, 862.

⁶ Swadener, *Jour. Amer. Med. Assoc.*, 1913, 60, 1479; Pierce, *Boston Med. and Surg. Jour.*, 1909, 160, 232.

⁷ Ring, *Trans. Amer. Ophth. Soc.*, 1902, 9, 529.

⁸ *Ophthalmic Record*, 1899, viii, 335.

⁹ Raub, *Ophth. Rec.*, 1899, 8, 169; Burnett, *Loc. cit.*; Buller and Wood, *Jour. Am. Med. Assoc.*, 1904, 43, 972, 1058, 1117, 1213, 1289.

¹⁰ Buller, *Montreal Med. Jour.*, 1904, 33, 29 (2 cases); Koller, *Med. Rec.*, 1905, 49, 10.

of methyl alcohol within three hours all would have marked abdominal distress, 4 would die, 2 of them becoming blind before death, 6 would eventually recover, of whom 2 would be permanently blind.

Fatal Period.—Death has usually occurred in from twenty-four to thirty-six hours; several cases have been reported in which it occurred between six and twenty hours, and in 1 case it is said to have occurred after one hour. It is often delayed for three or four days.

Treatment.—In cases of poisoning by methyl alcohol the stomach should be washed out; this should be repeated since some of the poison passes from the blood into the stomach. Stimulants, such as camphor and caffeine, seem to be indicated. Morphin may be necessary to relieve the pain. The eye symptoms have apparently been treated with some success by the use of pilocarpin, potassium iodid, strychnin, and cathartics.¹ Lumbar puncture has been highly recommended.²

Favorable results have been reported from the use of sodium bicarbonate by mouth or intravenously.³ The condition, however, is far more complicated than that of simple acid poisoning, and attempts to prevent death or prolong life by alkali treatment in animal experiments have as yet not proved very encouraging.⁴

Postmortem Appearances.⁵—Rigor is usually well marked; the blood is described as being of a dark cherry-red color and fluid, and a peculiar red lividity of the skin is reported. There is hyperemia of the mucous membrane of the stomach, and duodenum, and usually small hemorrhages; the lungs are hyperemic and edematous; edema and congestion of the brain and meninges with increase in the cerebrospinal fluid is reported; the mucosa of the bladder was found hyperemic in a number of cases.

CASES OF POISONING BY METHYL ALCOHOL

CASE 1.—Barber always temperate. Took by mistake in evening about 3 or 4 ounces of methyl alcohol. No symptoms until next morning, then headache and dim vision so that he could not see to do his work. Vision varied for several days; then "stone blind" for eight days; gradual improvement, and after about five weeks could see to work, then failed again. Six months later R. V. = fingers at 8 feet, L. V. = fingers at 3 feet; nerves atrophied; visual fields consisted of small excentric areas; condition permanent.⁶

CASE 2.—Four men began on Monday to varnish beer vats 12 or 15 feet high, closed, dark and airless, except for small openings. One man had already worked for three days of the preceding week; on Monday was dizzy; Tuesday evening walked as though intoxicated; Wednesday, sweating and vomiting; could not see well; totally blind when seen six days later, then slight improvement. The other three men worked a day longer (three days in all); one died on the fourth, another

¹ See Harlan, Gifford, and others, *Loc. cit.*

² Pincus, *Klin. Monatshft. f. Augenheilk.*, 1920, 65, 695.

³ Gettler and St. George, *Jour. Amer. Med. Assoc.*, 1918, 70, 145; Harrop and Benedict, *Ibid.*, 1920, 74, 25; Isaacs, *Ibid.*, 1920, 75, 718; Isaacs, *Ohio State Med. Jour.*, 1921, 17, 471.

⁴ Hunt (unpublished); Haskell, Hileman and Gardner, *Arch. int. Med.*, 1921, 27, 71.

⁵ Ströhmberg, *St. Petersb. med. Woch.*, 1904, 31, 55 (13 autopsies); cf. Wood, *New York Med. Jour.*, 1905, 81, 5; Pierce, *Boston Med. and Surg. Jour.*, 1909, 160, 237; Bachmann, *U. S. Naval Med. Bull.*, 1909, 3, 33; Isaacs, *Loc. cit.*; Norris, *New York Med. Jour.*, 1920, iii, 583.

⁶ Buller, *Montreal Med. Jour.*, 1904, 33, 29.

on the sixth day; the other showed symptoms of poisoning (reeling, headache, etc.), but recovered. In the fatal cases there were symptoms of intoxication, vomiting, chills, pain in eyes, dimness of vision, and unconsciousness.¹

CASE 3.—Man suffered from "rheumatism" in calves of legs and hips. Rubbed them with methyl alcohol twice, sometimes three times a day for a month or more. One morning after usual rubbing sight became dim; nausea; walked two miles to his house, which he barely recognized; totally blind within an hour. Pupils widely dilated, inactive to light; light perception lost. Transient improvement at times for one month or six weeks; then total blindness with atrophied nerves. Drinking of methyl alcohol almost certainly excluded.²

CASE 4.—A man on Sunday stole some Colonial spirits from the factory where he was employed. Through the day he drank a quantity of it, how much was not ascertained. Monday morning he worked as usual. Monday afternoon he felt sick and remained at home. He complained of headache, dizziness, vomiting, abdominal pains, a burning sensation in epigastrium and behind the sternum, and muscular weakness. During the evening he fell into a troubled sleep. He awoke about midnight and found he was totally blind. He was visited about 2 A. M. Tuesday; he was in bed, tossing from side to side, complaining bitterly of pain and weakness and nausea, and bemoaning his lost vision. His mind was absolutely clear; he said he "was done for." His skin was pallid and dusky. The pulse was weak and rapid and of poor volume. His respiration was labored. Probably the mental anguish was a factor. Suddenly a severe convulsion occurred and death ensued in a few moments.³

Isolation.—Methyl alcohol is isolated from tissues by distillation in a boiling-water bath by means of steam. (See p. 43.)

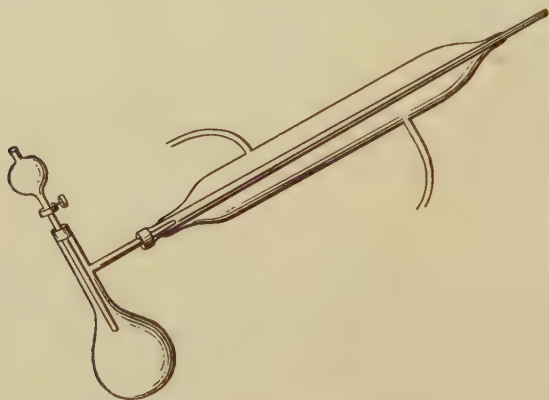


FIG. 59.—Apparatus for Riche and Bardy's Test.

Tests.⁴—1. **Method of A. Riche and C. Bardy⁵ and of K. Windisch.⁶**
—Fifteen grams of iodine and 2 grams red phosphorus are placed in a small 30 c.c. distillation flask which is set up with a condenser as in Fig. 59.

Ten c.c. of distillate are allowed to flow in through the dropping funnel, a violent reaction ensues, the condenser acting as a reflux. When action is over, heat flask five minutes in water-bath. Now place

¹ Wood, Jour. Amer. Med. Assoc., 1912, 59, 1962.

² Woods, Ibid., 1913, 60, 1762.

³ Pierce, Boston Med. and Surg. Jour., 1909, 160, 237.

⁴ Gettler, A. O., gives a comprehensive review of the various tests for methanol in the presence of ethanol, Jour. Biol. Chem., 1920, xlii, 311. See also Jansch, Vrtljschr. f. ger. Med., 1921, 62, 1.

⁵ Compt. Rend., 1875, 80, 1076.

⁶ Arbeiten aus dem Kaiserl. Gesundheitsamte, 1893, 8, 286.

the condenser in normal position, and distil off the alkyl iodids. Separate them from water, and place in a beaker containing 6 c.c. of freshly distilled anilin, and warm on bath to 50–60° C. (122°–140° F.). The mixture solidifies because of formation of (jodwasserstoffsaurem) dialkyl anilin. Now add hot water and boil up until a clear solution results. Then add KOH, which liberates the free bases. These bases are next oxidized. Two grams NaCl + 3 grams $\text{Cu}(\text{NO}_3)_2$ + 100 grams sand are mixed, dried at 50° C. (122° F.), and ground up well. Take 10 grams of this mixture in a test-tube, add 1 c.c. of the above bases mixed well with a rod and heat at 90° C. (194° F.) in a water-bath for ten hours. This product is now ground up fine, add 100 c.c. absolute alcohol and boil up, filter. Dissolve 1 c.c. of this filtrate in 500 c.c. water. In the presence of methyl alcohol this solution is violet; if ethyl alcohol only is present the solution gets slightly red.

2. Trillat Method.¹—To 50 c.c. of the material add 50 c.c. of water and 8 grams of lime, and fractionally distil by the aid of Glinksy bulb tubes. Dilute the first 15 c.c. of the distillate to 150 c.c., mix with 15 grams of potassium bichromate and 70 c.c. of sulphuric acid (1 : 5), and allow to stand for one hour with occasional shaking. Distil, reject the first 25 c.c., and collect 100 c.c. Mix 50 c.c. of the distillate with 1 c.c. of rectified dimethyl-anilin, transfer to a stout, tightly-stoppered flask, and keep on bath at 70° to 80° C. (158° to 176° F.) for three hours with occasional shaking. Make distinctly alkaline with sodium hydroxid, and distil the excess of dimethyl-anilin, stopping the distillation when 25 c.c. have passed over. Acidify the residue in the flask with acetic acid, shake, and test a few cubic centimeters by adding 4 or 5 drops of water with lead dioxid in suspension (1 gm. in 100 c.c.). If methyl alcohol be present, a blue coloration occurs which is increased by boiling. Ethyl alcohol thus treated yields a blue coloration, changing immediately to green, afterward to yellow, and becoming colorless when boiled.

3. Physical Properties.²—Determine at 20° C. (68° F.) the refraction of the distillate obtained in the determination of alcohol by the immersion refractometer. If, on reference to the table, the refraction shows the percentage of alcohol agreeing with that obtained from the specific gravity, it may be safely assumed that no methyl alcohol is present. If, however, there is an appreciable amount of methyl alcohol the low refractometer reading will at once indicate the fact. If the absence from the solution of refractive substances other than water and the alcohols is assured, this qualitative test, by difference in refraction, is conclusive.

4. Color Reaction.³—After specific gravity and refraction have been determined, take 20 c.c. of the distillate and boil for seven hours in a reflux apparatus with 15 grams of potassium hydroxid and 1 gram of

¹ Leach, Food Inspection and Analysis, 3d ed., p. 750; also Compt. Rend., 1898, 127, 232; 128, 438.

² Leach and Lythgoe, Jour. Amer. Chem. Soc., 1905, 27, 964.

³ Vivario, R., Jour. Pharm. Chim., 1914, vii, Series 10, 145 (abstract in Jour. Chem. Soc., 1914, cvi, 780).

hydroxylamin hydrochlorid. This produces cyanid if methyl alcohol is present. The mixture is then cooled, acidified with sulphuric acid, and distilled with steam. The distillate is tested as follows:

To 5 c.c. add a few drops of sodium hydroxid, a few drops of ferrous sulfate, and then ferric chlorid. Finally, acidify with hydrochloric acid; if cyanid is present, a Prussian-blue color results. To a second 5 c.c. portion add a few drops of sodium hydroxid, then add 2 or 3 c.c. of yellow ammonium sulfid, and evaporate to dryness on the water-bath. Cool and acidify with hydrochloric acid. Filter and add 1 c.c. of ferric chlorid. If a red color is produced, cyanid is present, indicating that methyl alcohol was originally present.

The above tests can be used only if at least a few cubic centimeters of the methanol itself is available. If menthanol is only present in small amounts, as in aqueous solution obtained by distilling brain tissue or liver tissue, the above methods are not applicable. For such purposes the methanol in solution is oxidized to formaldehyd, and tests for this substance are then applied (see under Formaldehyd). Oxidation to formaldehyd is brought about by sulphuric acid and a little potassium dichromate and distilling.

Quantitative Determination.—1. The addition of methyl to ethyl alcohol decreases the refraction in direct proportion to the amount present; hence the quantitative calculation is readily made by interpolation in the table, using the figures for pure ethyl and methyl alcohol of the same alcoholic strength as the sample.¹

Example.—Suppose the distillate made up to the original volume of the measured portion taken for the alcohol determination has a specific gravity of 0.97350, corresponding to 18.38 per cent. alcohol by weight, and has a refraction of 35.8 at 20° C. (68° F.) by the immersion refractometer; by interpolation in the refractometer table, the readings of ethyl and methyl alcohol corresponding to 18.38 per cent. alcohol are 47.2 and 25.4, respectively, the difference being 21.8; $47.2 - 35.8 = 11.4$; $(11.4 \div 21.8) 100 = 52.3$, showing that 52.3 per cent. of the alcohol present is methyl alcohol.

2. Micro Method.²—Dilute the solution, previously purified as necessary, to 1 per cent. by volume of total alcohol (Sample Solution A). Of this, pipet 10 c.c. into a 50 c.c. volumetric flask, add 10 c.c. of a 4 volume-per cent. solution of pure ethyl alcohol, and make up to the mark with water (Sample Solution B). Of the latter, likewise, dilute 10 c.c. (Sample Solution C). Into 50 c.c. tall-form Nessler tubes pipet 4 c.c. of the three sample solutions. Prepare standard methanol tubes containing, respectively, 1, 2, and 3 c.c. of a 0.04 volume-per cent. aqueous solution of pure methanol, plus 1 c.c. of 4 per cent. pure ethyl alcohol, plus sufficient water to make 4 c.c. After the tubes are properly arranged in a rack the following operations are put through in strict parallelism, remembering that each reagent is to be added to all tubes before any are mixed:

¹ Leach and Lythgoe, Jour. Amer. Chem. Soc., 1905, 27, 964.

² R. M. Chapin, Jour. Ind. and Eng. Chem., June, 1921.

1. Add 1 c.c. of 1 in 5 volume solution of syrupy phosphoric acid (C. P., 85 per cent.), and mix.

2. Add 2 c.c. of 3 per cent. potassium permanganate solution, mix, and let stand thirty minutes.

3. Add 1 c.c. of 10 per cent. oxalic acid solution, mix, and let stand till a clear brown color forms (about two minutes).

4. Add 1 c.c. concentrated H_2SO_4 (C. P.), mix, and let stand a few minutes for temperatures to become equal.

5. Add 5 c.c. Schiff-Elvove reagent,¹ mix well, and let stand till colors are sufficiently developed (one-half to two hours).

Each 1 c.c. of 0.04 per cent. methanol in the standard tubes is equivalent to volume percentages of methanol in total alcohol contained in the sample as follows:

Sample solution.	Per cent.
A.....	1
B.....	5
C.....	25

For more precise results the determination is repeated on the appropriate sample solution with more closely set standards. The sharpest results are obtained with standard tubes containing not over 1 c.c. of standard methanol. To bring the sample into this range it is often best to use only 2 c.c. of a sample solution, adding thereto 0.5 c.c. of 4 per cent. ethyl alcohol, and sufficient water to make 4 c.c. Approximate readings may be made after thirty minutes, precise ones after one hour, but best under two hours, for the colors fade later. The limit of detection is 0.2 c.c. of the standard 0.04 per cent. methanol.

ETHYL ALCOHOL

From almost every standpoint ethyl alcohol must be regarded as the most important poison with which medical men and jurists have to deal; no other poison causes so many deaths or leads to or intensifies so many diseases, both physical and mental, as does alcohol in the various forms in which it is taken. Yet the number of deaths due to acute alcoholism, with which we are especially concerned here, is comparatively small when the enormous number of cases of intoxication is taken into consideration. Baudy² reported 1129 hospital cases of alcoholism, acute and chronic, in which 14 died—a mortality of 1.5 per cent.; as many of these were chronic cases, in which the mortality is greater than in the acute, the death-rate in the latter is still smaller. Other hospital statistics show a higher death-rate, from 5 to 10 per cent., but the number of acute cases is not given. Six hundred and eighty deaths

¹ 0.2 gram finely powdered fuchsin is dissolved in about 120 c.c. of hot water and cooled to room temperature. Two grams of anhydrous sodium sulfite (U. S. P.) are dissolved in about 20 c.c. of water and are added to the fuchsin solution. Add to this mixture 2 c.c. HCl (sp. gr. 1.19) and dilute to 200 c.c. with water. After standing about one hour this solution is ready as a reagent (see Elvove, Jour. Ind. and Eng. Chem., 1917, 9, 295).

² Quarterly Jour. of Inebriety, 1900, 22, 58.

from alcohol were reported in New York City for the year 1916; in 1920 there were only 84.

In the registration area of the United States (which included 55.3 per cent. of the population of the U. S.) there were reported for 1908, 2025 deaths in the male population between the ages of twenty and seventy-four as due to "alcoholism." Phelps,¹ however, estimated that alcohol may have figured as a causative or contributory factor in 66,000 deaths in the United States in 1908, or 7.7 per cent. of the total adult mortality; similar estimates for Switzerland in 1900-1903 were that alcohol played a similar rôle in 10.3 per cent. of the deaths among adult males.

Properties.—Pure ethyl alcohol (alcohol ethylicum, ethanol, Alcohol Dehydratum, U. S. P., C_2H_5OH). "is a transparent, colorless, mobile, and volatile liquid having a characteristic odor, and a burning taste."² It is very hygroscopic. Specific gravity not higher than 0.797 at 15° C. (60° F.). It boils at 78.4° C. (173.1° F.), and is congealed at -130.5° C. (-202.9° F.). It burns with a non-luminous flame. It dissolves resins, fats, volatile oils, bromin, iodin, etc., also many salts and gases. On oxidation it is converted into aldehyd and acetic acid. The alcohol of commerce always contains some water (usually about nine parts by weight) and various impurities. The different alcoholic beverages vary widely in the percentage of alcohol they contain: beers have from 2 to 6 per cent.; light wines, from 7 to 12 per cent.; strong wines, such as port and sherry, from 15 to 20 per cent.; spirits, such as whisky, brandy, rum, and gin, have from 45 to 60 per cent. of alcohol by weight. It is the latter class of beverages (the spirits) that is responsible for most cases of acute poisoning with alcohol. These beverages, which contain in addition to ethyl alcohol higher alcohols of the same series, such as amyl alcohol or "fusel oil," and certain little-known bodies called "enanthic ethers" are, as a rule, slightly more poisonous than pure alcohol diluted to the same extent with water³; there is no justification, however, for the view, sometimes held, that the toxicity of these spirits is due more to the impurities than to the ethyl alcohol.

Physiologic Action.—Locally, alcohol is an irritant, producing redness and irritation of the skin especially if the vapor be confined, and a burning taste when swallowed. With large quantities the irritation of the stomach causes nausea and vomiting, and if the use is long continued, various pathologic changes result. Alcohol abstracts water from the tissues and precipitates proteins.

The views as to the action of alcohol after its absorption into the blood have undergone considerable change within recent years. Formerly alcohol was thought to be primarily a stimulant to the vascular, respiratory, and central nervous systems; now most pharmacologists hold that it is a depressant of these functions, and that the symptoms of stimulation are in reality due to a paralysis of inhibitory

¹ Phelps, 15th Int. Cong. Hygiene, 1912.

² United States Pharmacopeia, ix, 36, 1916.

³ See, e. g., Baer, Arch. f. (Anat. u.) Physiol., 1898, p. 295.

functions.¹ All are agreed that in large doses the action of alcohol is purely that of a depressant. Alcohol fulfils the theoretic requirements of a "food,"² but in only very exceptional cases is it to be regarded as a practicable food.³ After the administration of a moderate quantity of alcohol it is nearly all (usually more than 90 per cent.) oxidized in the body to carbon dioxid and water; the remainder is excreted largely by the lungs and kidneys. In cases of intoxication in man the blood contained about 0.13 per cent. alcohol.⁴ In animal experiments it is found that death ensues if the concentration of alcohol in the blood exceeds 6 parts per 1000. Alcohol passes readily into the testicles, prostate, ovary, and fetus⁵; it produces marked degenerative changes in the germ cells,⁶ and leads to defective offspring.⁷ It may reach a concentration in the milk equal to that in the blood,⁸ but it is very improbable that nurselings can be injured by this. The concentration in the urine is said to be the same as that in the blood.⁹ It probably passes into the cerebrospinal fluid; the amount of the latter and its pressure are increased.¹⁰

Two forms of poisoning with alcohol are recognized—acute and chronic. Certain acute symptoms occurring in chronic alcoholism are known as delirium tremens.

Acute poisoning with alcohol is frequently the result of a foolhardy attempt, often on a wager, to drink, within a certain short period, a large quantity of some distilled liquor; in this country, the beverage was usually whisky. In rare cases alcohol has been used for the purpose of committing murder (children¹¹) or suicide; children are sometimes poisoned by it accidentally. Poisoning has occasionally resulted from inhaling the vapors of alcohol.

In these days in which so many different kinds of factitious or illicit alcoholic beverages are obtainable in spite of the provisions of the XVIII Amendment, it is not surprising to find the number of cases of poisoning arising from the use of such drinks increasing to a great extent. However, the symptomatology of these cases is oftentimes quite different from that formerly noted. Reports from psychiatric hospitals indicate a different type of psychosis from that of

¹ Compare Dodge and Benedict, *Psychologic Effects of Alcohol*, Carnegie Inst., 1915. For other recent work on some of the physiologic effects of alcohol see Special Report Series Nos. 31, 34 and 56 of the Medical Research Committee, London, 1919-1920.

² For an excellent summary of this entire subject see Rosemann in Oppenheimer's *Handbuch der Biochemie*, 4, 413; also Tögel, Brezina and Durig, *Bioch. Zeits.*, 50, 296, 1913; Mellanby, *Proc. Roy. Soc. Med.*, 1920, 13, Sect. on Ther., 31.

³ Compare Hunt, *Studies in Experimental Alcoholism*, Bull. 33, Hyg. Lab., U. S. Public Health Service, 1907.

⁴ Schweisheimer, *Deut. Arch. f. klin. Med.*, 1912, 109, 271.

⁵ Nicloux, *Presse Méd.*, 1913, 21, 593.

⁶ Arlitt and Wells, *Jour. exp. Med.*, 1917, 26, 797.

⁷ Stockard and Papanicolaou, *Jour. exp. Zool.*, 1918, 26, 119.

⁸ Nicloux, *Compt. rend. de la Soc. de Biol.*, 1899, 51, 982.

⁹ Widmark, *Hygiea*, 1917, 79, 158. See, however, Miles, *Jour. Pharm. and Exp. Therap.*, 1922, 20, 265.

¹⁰ Schottmüller and Schumm *Neurol. Zentrbl.*, 1912, 31, 1020.

¹¹ Maschka, *Handbuch d. gericht. Med.*, 1881-82, ii, 384; abstracted by Blyth, *Poisons*, 4th ed., 1906, p. 144.

delirium tremens, which latter does not appear to be noted to any extent in these cases. In those cases resulting in death the exact causation is rather uncertain. While many, of course, die from the effects of the added wood alcohol, yet others show no symptoms of such poisoning. It is possible that the tolerance of many individuals to the effect of ordinary grain alcohol has been lost to a certain extent, and that these persons are simply overcome by the effects of the relatively large amount of alcohol which they imbibe when they have the opportunity; in other cases the greater concentration in which the alcohol may be taken (as in the use of some essences) may be a factor. On the other hand, many toxic factors, including in some cases denaturing agents not formerly found in alcoholic beverages, now find their way into these illicit drinks and may be accountable for fatal results. However this may be, it is apparently certain that there are relatively many more cases of poisoning from these drinks than were noted in the days before the adoption of the Volstead Act.

The **symptoms** of acute alcoholic intoxication depend upon a number of factors, such as the quantity and strength of the beverage taken, the rapidity with which it is taken, and the degree of tolerance which the person has established. In most cases of intoxication the first symptoms are a flushing of the face and hands, and a feeling of warmth; then comes the stage of excitement, the exact features of which are determined largely by the individual characteristics—some persons becoming sentimental, others angry, whereas others pass into a condition of stupor. Nausea, vomiting, dizziness, with a staggering gait and incoherent speech, and other symptoms of inco-ordination follow. The victim finally sinks into a deep, torpid sleep from which he may usually be aroused to some extent; the pupils are contracted if the subject is at rest, but dilate on stimulation; the muscles of the body are relaxed. In most cases recovery takes place within a few hours, but headache and nausea may persist for several days. After the ingestion of a very large quantity of alcohol the stage of excitement may be very brief or altogether absent; the patient falls into a deep comatose sleep; the face becomes pale or cyanotic and cold, the eyes injected and staring, the pupils contracted or dilated and scarcely reacting to light, the respiration slow, occasionally stertorous, the pulse first rapid, then slow and small. Involuntary evacuations of the feces and urine may occur. If the patient lives for a few hours, a marked fall of the body-temperature occurs, especially if he has been exposed to cold; such temperatures as 83° or 86° F. have been repeatedly reported, while in one case the rectal temperature sank to 75° F. The immediate cause of death is usually failure of the respiration. Convulsions frequently occur in children, rarely in adults.¹ Death frequently results not from the poison, but from the victim meeting with some accident due to the loss of consciousness: he may fall out of a window or into water, or food may be forced into the trachea during vomiting. The patient may die later of pneumonia contracted during the intoxi-

¹ See Cases 5 and 6.

cation. Many cases of sudden death occur in intemperate persons as a result of a slight excess in alcohol: in some cases the exact cause of death is not clear.¹ Long-continued illness may follow a single excess in alcohol.

Acute alcoholic insanity² or melancholia may develop in the course of an acute intoxication. In the former the person becomes maniacal and often commits deeds of violence, such as homicide, or he may vent his wrath on articles of furniture or on animals; in alcoholic melancholia there is often a tendency to suicide.

The **diagnosis** is usually easy, but opium and other forms of poisoning, apoplexy, and uremic coma have repeatedly been mistaken for acute alcoholism.

Fatal Dose.—The fatal dose of alcohol varies with the individual and his state of health, and with the strength of the beverage and the way in which it is taken. Some of the alcohol is usually returned in the vomit. Probably in the greater number of the fatal cases reported in the adult from 1 to 2 pints of whisky³ or brandy were taken; this would correspond to approximately 8 to 16 ounces (236 to 473 c.c.) of pure alcohol. In most cases, however, a smaller quantity would probably be fatal. From 3½ to 7 ounces (100 to 200 c.c.) of alcohol is usually considered the minimal fatal dose if taken in a concentrated form and at one time. Infants have died from 2 tablespoonfuls of brandy, and from 1 to 2 ounces (30 to 59 c.c.) of absolute alcohol (corresponding to from 2 to 4 ounces—59 to 118 c.c.—of whisky) would probably be fatal to most children under twelve years; yet one case is reported in which a child of three and a half years ultimately recovered after taking 12 ounces (355 c.c.) of whisky.⁴

Fatal Period.—The fatal period is variable, but death seems to have occurred in most cases in from six to ten hours after the beginning of the coma; it has occurred, however, within a few minutes, or been delayed for five or six days. Recovery is rare if the coma lasts longer than from ten to twelve hours. A low external temperature hastens the end.

Treatment.⁵—If vomiting has not taken place freely, this should be encouraged by the use of emetics or the stomach should be washed out with warm water. If collapse has occurred, the limbs should be rubbed and hot applications be made to the body. Care should be taken to maintain the body-temperature. Strong coffee, capsicum, or aromatic spirits of ammonia are recommended internally or strychnin and camphor hypodermically. Sleep or quiet may be induced by the bromids; opium should, as a rule, be avoided. In deep coma warm baths followed by cold affusions are useful; in extreme cases artificial respiration may be necessary. In alcoholic mania morphin and scopolamin are recommended. Lumbar puncture is said to relieve the headache and excitement.

¹ Hurd, Boston Med. and Surg. Jour., 1897, cxxxvii, 619.

² See Vol. I, page 568.

³ See Case 1.

⁴ See Case 6.

⁵ See Braunlich and also Crothers, Medical Record, 1900, lviii, 1024.

Postmortem Appearances.¹—In some cases of death due to acute alcoholism the stomach and other organs appear quite normal, but, as a rule, the stomach and esophagus are of a deep red color. There are often punctiform ecchymoses in the gastric mucous membrane which may also be easily separated. The contents of the skull are usually markedly hyperemic; there is frequently extravasation of blood in the brain and its membranes, and edema of the brain-substance or of the membranes. There may be a serous effusion in the ventricles of the brain. Edema of the lungs is frequent. Cadaveric rigidity may last unusually long. The contents of the stomach and the various organs, especially the brain, may have a well-marked odor of alcohol; if the weather is cold, this may last for a long time.

In chronic alcoholism the lesions may be marked or may be absent. Sometimes the dura mater is thick and closely adherent to the skull. The brain may be edematous, atrophied, or normal. The stomach and kidneys may show the lesions of chronic inflammation; the liver is frequently cirrhotic and fatty; the large vessels are usually atheromatous. Marked histologic changes occur in the cells of the brain and spinal cord.²

The subject of **chronic alcoholism** is best treated in works on general medicine, but a few words may be said about delirium tremens. Delirium tremens has been aptly characterized as only an incident in chronic alcoholism; it is especially common among those addicted to the use of distilled liquors. The attack frequently breaks out without any warning, but often it is precipitated by a temporary excess in alcohol, by an accident, by a surgical operation, or by an acute inflammation, particularly pneumonia. The attack usually begins with restlessness, sleeplessness, and tremors of the hands; then follow, in a day or two, the characteristic symptoms: hallucinations of sight, more rarely of sound, incessant movement, and incoherent muttering. The patients are anxious and frequently desire to go out, and constant watching is necessary to prevent them from jumping from windows or committing suicide in other ways. The hallucinations and illusions sometimes lead to homicidal attempts. The symptoms may subside in three or four days, or they may continue and the patient die from failure of the heart.

Sometimes a person who has suffered from delirium tremens, especially if he be an epileptic, enters into a condition of trance and may do things of which, later, he has no recollection.³

CASES OF POISONING BY ALCOHOL

CASE 1.—A moderate drinker, aged twenty-five, in apparent good health, wagered that he could drink 1 pint of whisky within ten minutes. He drank 1½ pints of cheap whisky and started for home. He soon became unconscious, vomited, and became comatose. His face was livid, he breathed heavily, and after four or five convulsions he died in six hours from the time of drinking the spirits. Autopsy, performed thirty-six hours after death, revealed the following: Pupils widely dilated

¹ See Case 1.

² Larkin and Jelliffe, *Medical Record*, 1899, lvi, 37.

³ See Francotte, *Journal de Neurologie et d'Hypnologie*, 1897, ii, 24; also numerous papers by Dr. Crothers, of Hartford.

and unequal; sinuses and pia engorged; whole brain edematous; lungs engorged and lower portions dotted with pleural ecchymoses. From the stomach 14.5 c.c. ($\frac{1}{2}$ ounce) of absolute alcohol were recovered; the liver contained 3.5 c.c. (55 min.).¹

CASE 2.—Laborer, aged thirty-three, drank between 10 and 15 ounces (295 to 444 c.c.) of whisky. He became intoxicated in twenty minutes, and fell to the ground in a deep sleep soon afterward. It was impossible to rouse him. The pupils were contracted to almost pin-point size until death took place nineteen hours later. Autopsy, thirty hours after death, showed: Rigor mortis complete; dura mater congested; no effusions in ventricles of brain.²

CASE 3.—Woman, aged forty-one, a periodic inebriate, drank $1\frac{1}{2}$ pints of exceptionally strong whisky. Found lying on back insensible in a few minutes; died five and a quarter hours later, without recovering consciousness. Pupils were dilated. Temperature fell to 7° F. below normal. At autopsy patches of mucous membrane of stomach were found semidetached; parts of walls were fiery red.³

CASE 4.—Girl, aged four, took 2 ounces (59 c.c.) of whisky. Pulmonary edema developed in eleven hours and led to death eleven hours later.⁴

CASE 5.—Girl, aged five, took quantity of whisky supposed to be but "2 dessertspoonfuls." Soon became insensible, and the use of artificial respiration became necessary at one time. After nine hours violent tetanic convulsions developed; these were relieved by chloral. Then came dyspnea, cyanosis, an increasing temperature (106.4° F.), and death after fifty-six hours. At autopsy brain was found to be normal; there was considerable bronchial secretion, but no pneumonia. Other organs were normal.⁵

CASE 6.—Child, aged three and a half, accustomed to small drinks of whisky. Said to have drunk at least 12 ounces (355 c.c.) of pure whisky in one afternoon. Fell into a kind of stupor lasting in varying degrees for more than two months. There were convulsions, right-sided paralysis, extreme contractures of the extremities due to multiple neuritis, strabismus, and repeated vomiting. Fever and symptoms of consolidation of the lower part of the right lung were also present. After about five months the child appeared to have recovered completely; there were no evidences that his mental condition had been impaired.⁶

Isolation.—Alcohol may serve as a type of a large group of substances whose common property of volatility with steam renders their separation from animal tissue a comparatively easy test. While the method employed is fundamentally a simple process of distillation, many complicated forms of apparatus have been devised, especially for the purpose of securing an effective fractional distillation, but also to avoid overheating the material or the loss of extremely volatile substances, such as chloroform and ether. Moreover, in the general application of the method it is necessary to observe certain precautions in order to prevent the occurrence of chemical alterations which might give rise to a confusion of the poison with its alteration products, or of deep-seated chemical decompositions in consequence of which the poison may altogether escape detection.⁷

But where the search is especially directed to alcohol, no serious difficulty can arise. After proper comminution the suspected material, if not already acid, is faintly acidified with tartaric acid and submitted to distillation by passing steam from a separate vessel. A simple and convenient form of apparatus is that represented in Fig. 3, p. 43.

The distillate is placed in an ordinary distilling flask, treated with

¹ Baker, *Quarterly Journal of Inebriety*, 1900, xii, 105.

² Berry, *Lancet*, 1893, i, 723.

³ Kerr, *Lancet*, 1895, i, 404.

⁴ Devine, *Boston Med. and Surg. Jour.*, 1895, cxxxiii, 545.

⁵ Weber, *Edinburgh Med. Jour.*, 1897, i, 631.

⁶ Herter, *New York Med. Jour.*, 1896, lxiv, 608.

⁷ Consult also p. 42 in section on General Principles of Toxicology.

pure magnesium oxid, and redistilled very slowly over the water-bath. This distillate is accurately measured, its specific gravity taken with a pycnometer, and after a convenient portion has been removed for a quantitative determination, is used for the tests given below.

A large proportion of the water may be removed from the product without loss of alcohol by distilling over potassium carbonate. If a complete dehydration be desired, a rather useless operation and one which necessarily involves serious loss of material—it should be noted that the use of calcium chlorid is entirely inadmissible; that calcium oxid acts violently on dilute alcohol, and that the last traces of water can best be removed by digestion with dehydrated copper sulphate.¹

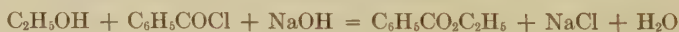
Tests.—1. When treated with an aqueous solution of iodine in potassium iodid and then with enough 10 per cent. sodium carbonate solution to remove the brown color, alcohol yields, especially on warming, a yellow crystalline precipitate of iodoform² which is easily identified by its odor and by the various hexagonal forms which it exhibits under the microscope (Fig. 60). This reaction is extremely sensitive and is not produced by ether nor by methyl alcohol.³ On the other hand, acetone, lactic acid, aldehyd, and a large number of substances will yield iodoform under the conditions stated.



Fig. 60.—Crystals of iodoform.

2. On shaking an aqueous solution of alcohol with a drop of benzoyl chlorid and decomposing the excess of the reagent by warming with a little caustic soda, the odor of ethyl benzoate can be detected,⁴ the irritating odor of the benzoyl chlorid disappearing, owing to its conversion into sodium chlorid and sodium benzoate.

3. When warmed with dilute sulphuric acid and potassium bichromate, aqueous solutions of alcohol give off aldehyd,⁵ which can be recognized by its odor, and the solution turns green from the formation of chromium sulphate—



3. When warmed with dilute sulphuric acid and potassium bichromate, aqueous solutions of alcohol give off aldehyd,⁵ which can be recognized by its odor, and the solution turns green from the formation of chromium sulphate—



If the escape of the aldehyd be prevented by working with a closed vessel, the alcohol is quantitatively oxidized to acetic acid, a reaction which forms the basis of an admirable quantitative method⁶:

¹ Soubeiran, Liebig's Annalen, xxx, 356; Erlenmeyer, Ibid., clx, 249.

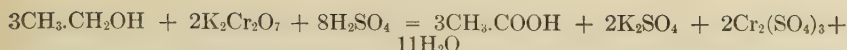
² Lieben, Ibid., Supp. 7, 218; Hager, Zeitschr. f. anal. Chem., ix, 492.

³ Lieben, Liebig's Annalen, Supp. 7, 377.

⁴ Baumann, Ber. d. d. chem. Ges., xix, 3218.

⁵ Liebig, Liebig's Annalen, xiv, 133.

⁶ Bourcart, Zeitschr. f. anal. Chem., xxix, 609.



4. Mix a little of the suspected solution with dry caustic potash and a few drops of carbon disulphid. When the excess of the latter has evaporated, add a drop of a neutral aqueous solution of ammonium molybdate and acidify with sulphuric acid. In the presence of alcohol a wine-red color will be produced.

5. If the suspected distillate is mixed with an equal volume of concentrated sulphuric acid, and then some solid sodium acetate is added and then warmed, the agreeable odor of ethylacetate appears.

6. A little of the distillate is oxidized by means of plunging a red hot copper spiral into it several times. After cooling, a little reduced fuchsin is added. Within one-half minute a red color develops. Distillates from cases in which no alcohol was taken when treated in the above manner give no red color even in five to ten minutes, or perhaps only a slight trace of pink. Distillates from badly decomposed tissue may, under the above treatment, yield with reduced fuchsin a red color, although no alcohol is present. This red color, due to putrefactive products, is more of a violet red however.

Estimation.—1 (*In Liquors*).—The distillation is carried out on a quantitative basis. The amount of alcohol is estimated by means of the specific gravity or refraction of the distillate.¹

2 (*In Tissue*).—Since Bechamp² has shown that alcohol is to be found normally in traces in the animal body, a quantitative estimation should form a part of every toxicologic examination. For this purpose the method of Bourcart is preferable to the older ones which are based on the oxidation of alcohol to acetic acid with platinum black.³

An aqueous solution containing about 0.5 per cent. of alcohol is heated in a closed tube on the water-bath with sulphuric acid, and a known quantity of a standard solution of potassium bichromate. The product is then treated with potassium iodid, and the liberated iodine titrated with a standard solution of sodium thiosulphate.

3. For determining the alcohol content in brain or liver tissue, the above method may not be applicable because the amount of alcohol present in either brain or liver is too small to admit determination by the above method.

The following microcolorimetric method is very convenient.⁴

Uniform and standard technic must be adhered to; 500 grams of finely divided tissue plus 500 c.c. of water are acidified with tartaric acid. This is carefully distilled with steam on a water-bath at a slow rate until no more alcohol comes over, as tested by the iodoform reaction. Usually between 300 and 400 c.c. of distillate bring this about, so that as a standard, 400 c.c. are now collected without testing. The

¹ Leach, Food Inspection and Analysis, 3d ed., 658, also 715.

² Bechamp, Zeitsch. f. anal. Chem., xx, 603.

³ See A. W. Blyth, Foods.

⁴ Personal communication. This method was developed and used by Dr. A. O. Gettler at the laboratories of Bellevue Hospital and of the Chief Medical Examiner's Office, New York City.

receiving flask is kept ice cold. This distillate is now put in a 500 c.c. flask, neutralized with MgO , and again distilled (without steam) on a gauze; this distillation should be carried out at a slow rate, about 4 to 6 drops a minute. Exactly 100 c.c. are collected. To this distillate is added 5 c.c. of concentrated sulphuric acid, mixed and cooled. Two c.c. of a 5 per cent. potassium dichromate solution are now added and the mixture is slowly distilled until 50 c.c. of distillate have been obtained. This 50 c.c. of distillate, as also 50 c.c. of standard obtained as outlined below, are each treated with 5 c.c. of reduced fuchsin solution.¹ The colors are allowed to develop for ten minutes and are then compared in a colorimeter.

The Standard.—Five c.c. of absolute alcohol are measured into a 100 c.c. volumetric flask and made up to mark with distilled water and thoroughly mixed; 5 c.c. of this 5 per cent. (by vol.) alcohol solution is added to 500 grams of finely chopped brain tissue, which has previously been proved to contain no alcohol. This is thoroughly mixed, placed in distillation flask, and distilled and treated in exactly the same manner as the unknown.

Calculation: $\frac{\text{Standard}}{\text{Unknown}} \times 20 = \text{mgs. alcohol in 500 gms. tissue.}$

HIGHER ALCOHOLS

The toxicity of the alcohols, at least in acute intoxication, increases up to a certain point with the size of the molecule: propyl alcohol is more toxic than ethyl alcohol, butyl alcohol more toxic than propyl, etc.; in the case of isomers, primary alcohols are more toxic than the secondary.²

The only members of these higher alcohols which have assumed importance in toxicology are those contained in the mixture known as **fusel oil** which consists chiefly of iso-amyl alcohol.

Fusel oil is used as a solvent for paints and in chemical industries; the inhalation of the vapors may cause headache and palpitation of the heart. Animal experiments show it to be about five times as toxic as ethyl alcohol. The amounts in whisky and other distilled spirits are too small to be an important factor in their toxicity.

A few cases of poisoning by fusel oil have been reported; 2 such cases, with a review of the literature on this subject, are described by Fletcher.³ The chief symptoms were profound unconsciousness of several hours' duration, and glycosuria lasting two or three days. Glycuronic acid was also found in the urine. In one case methemoglobin was found in the urine.

One of the amyl alcohols, tertiary amyl alcohol, has been used in medicine as a hypnotic under the name amylen hydrate and has caused

¹ E. Schmidt, *Lehrbuch der pharmazeutischen Chem.* 4, Auflage II, 307. Mix 20 c.c. of $NaHSO_3$ solution (1.27) with 1000 c.c. of fuchsin solution (1 : 1000) and then add 10 c.c. of pure concentrated HCl . This should discolorize in one hour. It should be kept in a well-stoppered bottle.

² Macht, *Jour. Pharmacol. exp. Ther.*, 1920, 16, 1.

³ Fletcher, *Amer. Med.*, 1901, 2, 210.

severe, and at least one case of fatal poisoning (35 gm. per rectum)¹; recovery followed 27 grams although there was unconsciousness for forty-eight hours²; also from 30 grams.³

Alcohol, Iso-amyl, $(\text{CH}_3)(\text{C}_2\text{H}_5) = \text{CH}-\text{CH}_2\text{OH}$.—The ordinary amyl alcohol (alcohol amylicum, U. S. P.).

Properties.—The iso-amyl alcohol found in fusel oil is a thin, oily liquid with a penetrating and oppressive odor, and a burning acrid taste. Its specific gravity is 0.818 at 15.5° C. (59.9° F.); it boils at 132° C. (269.6° F.). It is sparingly soluble in water but miscible in all proportions with alcohol, ether, benzene, petroleum, and benzin.

Isolation.—The finely ground tissue is distilled with steam as usual (see Ethyl Alcohol). The distillate, which is cloudy if fusel oil is present, is shaken out with ether. This ether layer is separated from the aqueous layer by means of a separatory funnel. The ether is then allowed to evaporate spontaneously. The fusel oil remains behind in the form of oily drops with characteristic odor. This oily residue is then further tested as indicated below. For extracting the iso-amyl alcohol from the distillate, chloroform can be substituted for ether. When working with whiskies they should first be diluted to about 10 per cent. alcoholic content and then shaken out with chloroform. This chloroform layer is separated from the aqueous layer and the chloroform is allowed to evaporate, leaving the fusel oil behind.

Tests.—1. *Odor Test.*—Fusel oil has a characteristic odor which one can always detect if isolated and put into a concentrated form as stated above. To make this test on whisky or other liquors, it is necessary to allow only 5 c.c. of the liquid to spread itself all over the inside surface of a wine glass. Then swing the glass through the air a few times. This enables the ethyl alcohol to evaporate quickly, leaving behind the fusel oil with its characteristic odor.

2. To some of the suspected material add twice its volume of concentrated sulphuric acid and warm slightly; a red color develops.

3. To some of the suspected material add a little sodium acetate and then some concentrated sulphuric acid and warm the mixture; iso-amyl acetate is produced, which has a characteristic pear odor.

4. *Marquardt's Test.*—To a drop or two of the suspected material in a test-tube add a little water, then a few drops of sulphuric acid, and finally a few drops of potassium permanganate solution (1 : 1000) until a little red color persists. Now cork up the test-tube and allow to stand twenty-four hours. During this period the red color of the permanganate vanishes and a few drops more should be added from time to time. At each removal of the stopper an odor is perceived, at first of valeric aldehyd, then of amylvalerianate, and finally, of valerianic acid.

5. *Uffelmann's Test.*⁴—To the suspected material add four times

¹ Jacobi and Speer, *Therap. Halbmonatshft.*, 1920, 34, 495.

² Anker, *Therap. Monatsheft.*, 1892, 6, 623.

³ Lowenstein, *Bioch. Zeitsch.*, 1906, 2, 111.

⁴ *Arch. f. Hygiene*, 1886, v, 229.

its volume of a freshly prepared methyl-violet solution which is made green by the addition of hydrochloric acid (1 part methyl-violet, 100 parts of water, and enough 0.2 per cent. HCl till decidedly green). If fusel oil is present reddish-violet drops appear at once on the green fluid. This test is to be recommended when the material to be tested has present other strongly odorous substances, thus hiding the odor of fusel oil and its oxidation products.

Estimation.—1. *Method of Röse—Stutzer and Reitmair—E. Sell.*¹—Chloroform is placed into apparatus (Fig. 61) up to 20 c.c. mark. The suspected liquor is diluted to 24.7 per cent. alcoholic content and 100

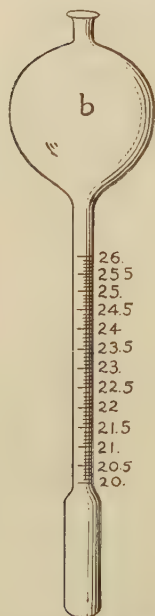


FIG. 61.—Röse-Herzfeld apparatus, for determining fusel oil.

c.c. of this are added to the chloroform. These are now well shaken together and the two layers are allowed to separate completely. The chloroform layer at the bottom shows an increase in volume. This is due to the taking up of some ethyl alcohol and practically all of the amyl alcohols. In order to deduct the increase in volume due to ethyl alcohol, this test is repeated with a fresh portion of chloroform and 24.7 per cent. pure alcohol in water. The increase in volume here is due to the ethyl alcohol only and if done under the same conditions this can be subtracted from the value obtained in the unknown. The difference will be the increase in the chloroform layer, due to fusel oil. If the liquor in question contains ethereal oils and esters, it should first be made alkaline with NaOH and then distilled. This is done in order to do away with the disturbing influence of these substances on this determination.

2. *Method of Mitchell and Smith.*²—Add to 100 c.c. of whisky 20 c.c. of half-normal sodium hydroxid, and saponify the mixture by boiling for one hour under a reflux condenser.³ Connect the flasks with a distilling apparatus, distill 90 c.c., add 25 c.c. of water, and continue the distillation until an additional 25 c.c. is collected.

Approximately saturate the distillate with finely ground sodium chlorid, and add a saturated solution of sodium chlorid until the specific gravity is 1.10.

Extract this salt solution four times with carbon tetrachlorid,⁴ using 40, 30, 20, and 10 c.c. respectively, and wash the carbon tetra-

¹ Bericht über 4th Versamml. bayer. Vertreter der angewandten Chemie, 1885.

² Leach, Food Inspection and Analysis, 3d ed., 748; also A. O. A. C. Proc., 1908, U. S. Dept. Agric., Bur. of Chem., Bull. 122, 199.

³ Or 100 c.c. of the liquor may be mixed with 20 c.c. of half-normal sodium hydroxid, allowed to stand overnight at room temperature, and distilled directly.

⁴ Purify 5 liters of carbon tetrachlorid by boiling for several hours under a reflux condenser with 200 c.c. of sulphuric acid and 25 grams of potassium bichromate in 200 c.c. of water; separate from the oxidizing mixture by distillation, and redistill over barium carbonate.

chlorid three times with 50 c.c. portions of a saturated solution of sodium chlorid, and twice with saturated solution of sodium sulphate.

To the carbon tetrachlorid extract, contained in the separatory funnel, add 10 c.c. of potassium hydroxid solution (1 : 1). Cool the mixture in ice-water to approximately 0° C. (32° F.). Similarly cool 100 c.c. of a solution of potassium permanganate solution (20 gm. to the liter), accurately measured in a flask. To the contents of the separatory funnel add the bulk of the permanganate solution, but without rinsing, retaining the residue to be added at a later stage. Remove the mixture from the bath, and shake vigorously for five minutes; set aside for thirty minutes, with occasional shaking, permitting the liquid to warm to room temperature (20° to 25° C.—68° to 77° F.). Accurately measure into a liter Erlenmeyer flask 100 c.c. of a solution of hydrogen peroxid slightly (about 2 per cent.) stronger than the permanganate solution, acidulate with 100 c.c. of an approximately 25 per cent. sulphuric acid solution, and slowly add the contents of the separatory funnel with constant shaking, keeping the acid solution constantly in excess. Rinse the separatory funnel and the flask containing the residue of permanganate with water and add to the peroxid solution. Finally, titrate the excess of hydrogen peroxid with standard potassium permanganate solution (10 gm. to the liter).

Run a blank determination, using the same amounts of the stronger permanganate, potassium hydroxid, hydrogen peroxid, the sulphuric acid solutions, and titrating the residual peroxid with the standard potassium permanganate as before.

The difference in the amounts of permanganate consumed in grams, times 0.696, gives the amount of amyl alcohol.

Alcohol, Tertiary Amyl, $(\text{CH}_3)_2 = \text{C}(\text{OH}) - \text{CH}_2 - \text{CH}_3$. — Dimethyl-ethyl carbinol.

Properties.—It is a colorless liquid boiling at 102.5° C. (216.5° F.) and having an odor similar to camphor.

Isolation.—General method of distillation (see Ethyl Alcohol).

Tests.—1. Odor is more like paraldehyd. 2. On oxidation, according to Marquardt's method (see under Tests for Amyl Alcohol), it yields acetic acid and acetone (see below).

Acetone $(\text{CH}_3\text{COCH}_3)$.—Dimethyl ketone (Acetonum, U. S. P.).

Properties.—A colorless liquid, odor somewhat like peppermint, boiling at 56° C. (132.8° F.). It is soluble in water.

Isolation.—By the general method of distillation with steam.

Tests.—1. A little of the suspected distillate is made alkaline and a potassium iodid solution of iodine is added gradually until the yellow color just barely disappears. Iodoform results with its characteristic odor and typical crystals.

2. Upon the addition of dilute sodium nitroprussid solution and a little sodium hydroxid a red color develops. If this is now acidified with acetic acid it changes to a cherry red.

Estimation.—Finely ground tissue (500 grams) are distilled with steam until all the acetone is in the distillate. Toward the end of

distillation a few drops of distillate are tested by the iodoform test to see if any more acetone is coming over; 15 c.c. of this distillate are placed in a 500 c.c. measuring flask. Add 10 c.c. of a 50 per cent. sulphuric acid and 35 c.c. of a 10 per cent. mercuric sulphate and mix. Connect the flask with a reflux condenser and heat to boiling. When boiling has begun add 5 c.c. of a 5 per cent. dichromate through condenser tube. Continue boiling one and a half hours. The precipitate which forms is a mercury sulphate chromate compound of acetone. The precipitate is collected on a Gooch crucible, washed with cold water, dried at 110° C. (230° F.) for one hour, and weighed; 20 mg. of precipitate represent 1 mg. of acetone.

FORMALDEHYD

Formaldehyd (HCHO) is a colorless irritant gas, prepared by the oxidation of methyl alcohol. It is freely soluble in water. The Liquor Formaldehydi, Solution of Formaldehyd (U. S. P.), contains "not less than 37 per cent. by weight" of formaldehyd with varying amounts of methyl alcohol. "Formalin" is a proprietary name for a similar solution.

Formaldehyd has been very extensively used as a preservative for milk and other articles of food; there has been much discussion as to the effect of the quantities ordinarily used for this purpose upon the individuals taking such articles of food; such use is generally prohibited by law in the United States.

The vapor of formaldehyd is very irritating to the mucous membranes, and workmen engaged in manufacturing it and those who use it in disinfecting houses often suffer severely from coryza, conjunctivitis, and bronchitis. Moreover, it has been found that animals are killed when confined in a room, the air of which contains the vapor in sufficient quantity to act as an efficient germicide.¹

Aqueous solutions containing 1 part of formaldehyd in 2000 are very irritating to the skin; long-continued application of strong solutions leads to ulcerations and gangrene; weak solutions lead to eczema.²

A few cases of poisoning have been reported from the swallowing of "formalin" or of the official solution.³ The **symptoms** resulted in part from the local irritating action upon the mouth, throat, and stomach (intense pain, vomiting, sometimes long continued; sometimes diarrhea), and respiratory passages (with eosinophilia⁴), and in part from an action upon the central nervous system; the latter may resemble those of acute alcoholic intoxication⁵: vertigo, stupor, unconsciousness, coma, also convulsions. There may be suppression of the urine for nineteen or twenty-four hours.⁶ Death resulted in two and a half hours after taking 30 c.c. (1 oz.) of "formalin"⁷; in thirty-two hours

¹ Harrington, *Amer. Jour. Med. Sci.*, 1898, 115, 69.

² Fisher, *Brit. Jour. Derm.*, 1901, xiii, 306.

³ MacLachlan, *Cleveland Med. Jour.*, 1909, 8, 606.

⁴ Trenkel, *Inaug. Diss.*, Munich, 1917.

⁵ Kluber, *Münch. med. Woch.*, 1900, 47, 1416.

⁶ Zorn, *Ibid.*, 1902, xlix, 1588.

⁷ Watt, *Brit. Med. Jour.*, 1912, ii, 350.

after taking from 1 to 3 ounces (30–90 c.c.) of a 4 per cent. solution of formaldehyd.¹ Recovery followed the taking of $\frac{1}{2}$ ounce (15 c.c.) of the 40 per cent. solution; also 60 to 70 c.c. ($2-2\frac{1}{3}$ oz.) of the 35 per cent. solution²; also, with prompt treatment (emetics) of $3\frac{1}{3}$ ounces (100 c.c.)³; also 4 ounces (120 c.c.) of a 37 per cent. solution.⁴

In cases of poisoning by formaldehyd solution, the administration of a dilute solution of ammonia or of the solution of ammonium acetate has been recommended; these unite with formaldehyd to form the non-irritating and non-toxic hexamethylenamin. Such treatment seems to have given good results.⁵

Properties.—A colorless, irritating gas which is strongly antiseptic, condenses at -20°C. (-4°F.), into a colorless liquid, solidifies at -90°C. (-130°F.), and is soluble in water.

On heating formaldehyd with dilute caustic alkali it splits into methyl alcohol and formic acid: $2\text{CH}_2\text{O} + \text{KOH} = \text{CH}_4\text{O} + \text{H}-\text{COOK}$, and on standing with ammonia it yields hexamethylenetetramin: $6\text{CH}_2\text{O} + 4\text{NH}_3 = (\text{CH}_2)_6\text{N}_4 + 6\text{H}_2\text{O}$. On standing with calcium hydrate formaldehyd yields a mixture of sugars, $\text{C}_6\text{H}_{12}\text{O}_6$ (Loew's formose), and with protein bodies (not with peptones) it forms insoluble elastic masses, and with gelatin, insoluble brittle masses called glutil.

Formalin, formol, is a 35 per cent. watery solution; **formalithe** is infusorial earth impregnated with 40 per cent. formaldehyd solution; **ichthoform** is a combination with ichthyol, and **tannoform**, a compound with tannin.

Isolation.—General method of distillation. The formaldehyd comes over in the first 20 to 25 c.c. portion of the distillate.

Tests.⁶—1. To 2 c.c. of the material add 1 c.c. of concentrated sulphuric acid, cool, and add 5 c.c. of reduced fuchsin solution; mix and allow to stand. The presence of formaldehyd is indicated by the violet-red color which gradually develops.

The fuchsin solution is made as follows: Dissolve 0.5 gram of fuchsin in 200 c.c. of distilled water; add an aqueous solution of sulphur dioxid, the quantity corresponding to 1 gram of sulphur dioxid gas; allow to stand until the solution assumes an amber color (this requires about one hour). The colorless fuchsin bisulphite solution which is obtained when more than 1 gram of sulphur dioxid is added to 0.5 gram of fuchsin is valueless as a reagent after standing two days. A solution prepared as outlined will keep well for ten days, although it is recommended not to use a solution after seven days.⁷

2. To 3 c.c. of distillate add 5 c.c. of concentrated sulphuric acid; mix; cool. Then add a few milligrams of morphin. A violet-red color develops if formaldehyd is present.

¹ Bock, Indiana Med. Jour., 1899, 18, 122.

² Gerlach, Münch. med. Woch., 1902, xlix, 1503.

³ Hoyt, Jour. Amer. Med. Assoc., 1910, 54, 1202.

⁴ Hale, Jour. Amer. Med. Assoc., 1922, 78, 452.

⁵ André, Jour. de Pharm. et Chimie, 1899, 6 s., 10, 10.

⁶ Gettler, A. O., gives a complete list of references on methanol and formaldehyd tests. Jour. Biol. Chem., 1920, xlii, 311.

⁷ See Schiff-Elvove reagent under Methyl Alcohol, p. 613.

3. To 3 c.c. of distillate add 3 c.c. of milk, then add a drop of very dilute ferric chlorid and 5 c.c. of concentrated hydrochloric acid. The mixture is then placed in a boiling water bath. A violet color develops if formaldehyd was originally present in the tissue examined. Although this test is unreliable when examining liquors, it is quite trustworthy and characteristic when working with tissues. This is probably due to the organism having destroyed or conjugated and excreted the interfering substances originally present in liquors.

4. To 3 c.c. of distillate add 5 or 6 drops of a saturated alcoholic solution of gallic acid and stratify some concentrated sulphuric acid underneath the mixture. A green to blue ring develops if formaldehyd is present.

5. To 2 c.c. of suspected liquid are added 10 drops of a 5 per cent. solution of phenylhydrazin hydrochlorid, 1 drop of a 0.5 per cent. sodium nitroprussid solution, and 10 drops of 10 per cent. sodium hydroxid solution. If formaldehyd is present, a blue color is obtained which changes to green and then to yellowish red. Acetaldehyd produces a red color.

6. Ten c.c. of the distillate are put into a small evaporating dish; 10 c.c. of strong ammonia are then added. The mixture is evaporated, just to dryness, on the water-bath. The formaldehyd condenses with the ammonia to hexamethylenetetramin. The latter is then dissolved in a few drops of water. A drop of mercuric chlorid is added to a small amount of this solution and placed on a microscopic slide. Typical crystals of hexamethylenetetramin-mercuric chlorid develop. The shape of these crystals varies with the concentration. It is, therefore, best to make control experiments for comparison with the suspected material.

7. Acidify a portion of the distillate with sulphuric acid, add a few drops of dimethylanilin, and heat at 40° C. (104° F.) for an hour or two in a sealed tube. Make the product alkaline with sodium carbonate and evaporate the excess of dimethylanilin. Acidify with acetic acid, and add a trace of lead dioxid, when the presence of formic aldehyd will be shown by the production of an intense blue color.¹

8. To a portion of the distillate are added twice its volume of alcohol and a few drops of diphenylenedihydrazin hydrochlorid. On warming, the solution is colored yellow, and on standing a while a yellow crystalline precipitate is formed.² This reaction is characteristic of formic aldehyd.

9. Heat a portion of the distillate with an equal volume of 40 per cent. caustic potash which contains 5 per cent. of resorcin. The presence of formic aldehyd is shown by the production of a red color.³

Estimation.⁴—1. **Potassium Cyanid Method.**—To 100 grams of material add 1 c.c. of 1 : 3 sulphuric acid and subject to distillation

¹ Trillat, Chem. Centralbl., 1898, ii, 585.

² Neuberg, Ber. d. d. chem. Gesel., xxxii, 1962.

³ Lebbin, Chem. Centralbl., 1899, i, 641.

⁴ Leach, Food Inspection and Analysis, 3d ed., 181, 825.

in a 500 c.c. Kjeldahl nitrogen flask, using a low circular evaporating burner to avoid frothing. According to Smith,¹ the first 20 c.c. of the distillate, or one-fifth the original volume, contain very nearly one-third of the total formaldehyd. Collect 20 c.c. of the distillate and determine the formaldehyd therein by the potassium cyanid method as follows²:

Treat 10 c.c. of tenth-normal silver nitrate with 6 drops of 50 per cent. nitric acid in a 50 c.c. flask, add 10 c.c. of a solution of potassium cyanid containing 3.1 grams of KCN in 500 c.c. of water, and make up to the 50 c.c. mark. Shake, filter, and titrate 25 c.c. of the filtrate with tenth-normal ammonium sulphocyanate, using ferric chlorid as an indicator.

Acidify another portion of 10 c.c. of tenth-normal silver nitrate with nitric acid, add 10 c.c. of the potassium cyanid solution to which the above 20 c.c. of the formaldehyd distillate has been added. Make up the whole to 50 c.c., filter and titrate as before 25 c.c. of the filtrate with tenth-normal ammonium sulphocyanate for the excess of silver.

The amount of potassium cyanid used up by the formaldehyd in terms of tenth-normal ammonium sulphocyanate, is found by multiplying by 2 the difference between the two results, and the total formaldehyd is calculated by multiplying by 3 the amount found in the 20 c.c. of distillate.

The reaction that takes place between the formaldehyd and the potassium cyanid probably results in the formation of an addition product as follows:



2. Ammonia Method.³—Weigh 10 grams of the formaldehyd solution into a flask, and treat with an excess of ammonia. Cork the flask and shake frequently during several days. The formaldehyd is by this process converted into hexamethylenamin.

Transfer the solution to a tared platinum dish, and evaporate nearly to dryness on the top of a closed water-bath. Finally the dish is transferred to a desiccator, and the drying continued over sulphuric acid to constant weight. The percentage of formaldehyd is calculated from the weight of the hexamethylenamin, making a correction for the residue left by the formaldehyd itself by direct evaporation: $6\text{CH}_2\text{O} + 4\text{NH}_4\text{OH} = (\text{CH}_2)_6\text{N}_4 + 10\text{H}_2\text{O}$. Or an excess of a standard ammonia solution may be added in the first place, the excess of ammonia being distilled off and titrated with standard acid, calculating the percentage of formaldehyd by the amount of ammonia absorbed.

3. Iodometric Method.⁴—Mix 10 c.c. of the aldehyd solution (diluted if necessary to a strength not exceeding 3 per cent. of formaldehyd) with 25 c.c. of tenth-normal iodine solution, and add drop by drop a solution of sodium hydroxid, till the color of the liquid becomes clear

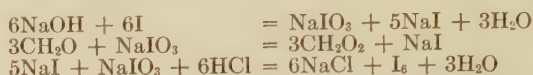
¹ Smith, Jour. Amer. Chem. Soc., 1903, 25, 1032, 1037.

² Zeits. anal. Chem., 36, 18-24.

³ Conn. Exp. Sta., Annual Report, 1899, 143.

⁴ Zeits. anal. Chem., 1897, 36, 18-24; abs. Analyst, 22, 221.

yellow. The solution is set aside for at least ten minutes, after which hydrochloric acid is added to set free the uncombined iodine, and the latter is titrated back with tenth-normal thiosulphate. Two atoms of iodine are equivalent to 1 molecule of formaldehyd, in accordance with the following reactions:



PARALDEHYD

Acute fatal poisoning with paraldehyd is very rare; death has, however, occurred from accidental overdoses.¹ It has apparently been used as a means of committing suicide.² Cases of chronic poisoning with paraldehyd are more common, as some individuals use it as others do alcohol, morphin, chloral, etc.

Properties.—Paraldehyd (Paraldehydum, U. S. P., $[\text{CH}_3\text{CHO}]_3$), a polymer of acetaldehyd, is a colorless liquid having a strong and characteristic odor and a burning, disagreeable taste. It boils at 124°C . (255.2°F). It is soluble in water (1 in 8), in alcohol, and ether, and solidifies when subjected to cold.

The physiologic action of paraldehyd is very similar to that of chloral, but it causes less depression of the circulation and respiration. The drug is eliminated by the lungs and kidneys; it imparts a very characteristic and disagreeable odor to the breath. Tolerance for paraldehyd is rapidly established.

Symptoms.—After an average dose the effects are those of the simple hypnotics, with little cardiac or respiratory depression; its action is very rapid. Larger doses occasionally cause nausea, vomiting, headache, and dizziness. After a very large dose there are deep stupor and complete relaxation of the muscles, as seen in persons under the influence of chloroform; the face is flushed, and the pupils are somewhat contracted. This condition may continue for many hours (thirty-four in one case³), and recovery take place.

The symptoms in chronic paraldehyd poisoning are various. There are usually disturbances of the digestion, thirst, emaciation, general muscular weakness, and mental failure, with tremors of the hands and tongue. Skin eruptions similar to those caused by chloral hydrate are common. There is usually insomnia, and there may be discontent, confusion, temporary loss of memory, hallucinations, and delusions of persecution.⁴ The symptoms resemble in some respects those of chronic alcoholism, and a condition not very unlike that of delirium tremens may result.⁵ A condition of euphoria not unlike that following morphin has been described.⁶

¹ O'Brien case, *Lancet*, 1890, ii, 423.

² Paltauf, *Wien klin. Wochenschr.*, 1893, 6, 888.

³ MacKenzie, *Brit. Med. Jour.*, 1891, ii, 1254.

⁴ Elkins, *Quarterly Jour. of Inebriety*, 1894, xvi, 333.

⁵ Fornaca and Quarelli, *Berl. klin. Woch.*, 1912, 49, 2451.

⁶ Hartz, *Jour. Amer. Med. Assoc.*, 1912, 58, 625.

Little is known as to the **fatal dose** and the **fatal period** of paraldehyd. Six or 7 drams (22.5–26 c.c.) given to a patient delirious from typhoid fever caused unconsciousness in five minutes and death in four hours¹; 3½ ounces (104 c.c.) caused severe, but not fatal, poisoning.² Those accustomed to the use of paraldehyd can take enormous doses; thus a woman learned to take from 16 to 18 ounces (473 to 532 c.c.) of the “elixir of paraldehyd” in twenty-four hours.³ Doses of 1 ounce (30 c.c.) have been taken for months without causing any symptoms; on the other hand, 2 ounces (59.2 c.c.) a day have led to the most severe symptoms.⁴

The **treatment** of both acute and chronic poisoning by paraldehyd is on the same general lines as that of poisoning by chloralhydrate.

The **postmortem appearance** of the stomach seems to resemble that caused by rather dilute alcohol⁵; the odor of the poison or of its decomposition products may be noticed.

ACETALDEHYD (CH_3CHO)

Properties.—Colorless irritating liquid having a peculiar odor and boiling at 21° C. (69.8° F.), and oxidizing in the air into acetic acid.

Isolation.—General method of distillation (p. 619).

Tests.—1. Into a clean test-tube, preferably rinsed out with a dilute solution of sulphurous acid, place 2 parts of the liquid or distillate to be tested and add 1 part of colorless fuchsin solution, and insert cork into test-tube. The development of a red color within two or three minutes indicates the presence of aldehyd.

2. To some of the suspected fluid add a little of a 1 to 10 solution of m-phenylendiamin chlorhydrate in freshly boiled air-free water. If aldehyd is present a yellow to red color develops within four minutes. After a longer interval a green fluorescence sets in. This reaction, according to K. Windisch, is sensitive to 0.001 per cent.

3. Ten c.c. of distillate are treated with 1 c.c. of ammoniacal silver nitrate solution and allowed to stand in the dark. The reduction of the silver salt to a black precipitate or to a silver mirror deposit indicates the presence of aldehyd.

4. A few drops of Nessler solution added to some of the distillate will produce a yellow or yellowish-red precipitate. No ammonia must be present when this test is applied. This test is sensitive to 1 in 400,000 (K. Windisch).

5. Tests of differentiation from formaldehyd⁶ (see under formaldehyd).

¹ O'Brien case, *Lancet*, 1890, ii, 423.

² MacKenzie, *loc. cit.*

³ Goodman, *American Practitioner and News*, 1890, 10, 289.

⁴ Reinhold, *Therap. Monatsh.*, 1897, ii, 300.

⁵ Paltauf, *Loc. cit.*

⁶ E. Schmidt, *Lehrbuch der pharmazeutischen chemie*, 4 Auflage II, 307. Mix 20 c.c. of NaHSO_3 solution (1.27) with 1000 c.c. of fuchsin solution (1 : 1000) and then add 10 c.c. of pure concentrated HCl. This should decolorize in one hour. It should be kept in a well-stoppered bottle.

Metalddehyd, prismatic crystals, subliming at 112°C . (233.6°F .), on heating with dilute acid is retransformed into acetaldehyd.

Paralddehyd, colorless liquid, boiling-point of 124°C . (255.2°F .), is soluble in alcohol, ether, and 9 parts of water.

These two polymers of acetaldehyd, when present, will pass over as acetaldehyd during the distillation from an acidified solution. The distillate is then tested for acetaldehyd (which see). To differentiate between paralddehyd and acetaldehyd, the strong and characteristic odor of the former is made use of.

Estimation.—1. **Reagents.**—(a) *Alcohol Free from Aldehyds.*—Prepare by first redistilling the ordinary 95 per cent. alcohol over caustic soda or potash, then add from 2 to 3 grams per liter of m-phenylenediamin hydrochlorid, digest at ordinary temperature for several days (or reflux on the steam-bath for several hours), and then distill slowly, rejecting the first 100 c.c. and the last 200 c.c.

(b) *Sulphite-fuchsin Solution.*—Dissolve 0.50 gram of pure fuchsin in 500 c.c. of water, then add 5 grams of SO_2 dissolved in water; make up to a liter, and allow to stand until colorless. Prepare this solution in small quantities, as it retains its strength for only a very few days. (See Schiff-Elvove reagent, p. 613.)

(c) *Standard Acetic Aldehyd Solution.*—Prepare according to the directions of Vasey¹ as follows: Grind aldehyd ammonia in a mortar with ether and decant the ether. Repeat this operation several times, then dry the purified salt in a current of air and finally in a vacuum over sulphuric acid. Dissolve 1.386 gram of this purified ammonium aldehyd in 50 c.c. of 95 per cent. alcohol, to this add 22.7 c.c. of normal alcoholic sulphuric acid, then make up to 100 c.c. and add 0.8 c.c. to compensate for the volume of the ammonium sulphate precipitate. Allow this to stand over night and filter. This solution contains 1 gram of acetic aldehyd in 100 c.c. and will retain its strength.

The standard found most convenient for use is 2 c.c. of this strong aldehyd solution diluted to 100 c.c. with 50 per cent. alcohol by volume. One c.c. of this solution is equal to 0.0002 gram of acetic aldehyd. This solution should be made up fresh every day or so, as it loses its strength.

2. **Process.**—Determine the aldehyd in the distillate. Dilute from 5 to 10 c.c. of the distillate to 50 c.c. with aldehyd-free alcohol (50 per cent. of volume), add 25 c.c. of the fuchsin solution, and allow to stand for fifteen minutes at 15°C . The solutions and reagents should be at 15°C . (59°F .) before they are mixed. Simultaneously prepare standards of known strength in the same way. Compare the red color developed in the unknown with that in the standard. From this the amount is calculated.

¹ Analysis of Potable Spirits, 30.

CHLORAL HYDRATE ¹

Most cases of poisoning with chloral are accidental. Of 136 cases collated by Witthaus,² 104 were accidental, 28 suicidal, and 4 criminal. Of 127 deaths due to chloral in England and Wales from 1883 to 1892, 111 were accidental, 15 suicidal, and 1 due to murder. The earlier accidental cases were due for the most part to physicians prescribing the drug in too large doses or to their administering it to patients having weak hearts; the later ones, to patients taking the drug without professional advice, or to mistakes. Chronic chloral poisoning is not uncommon; it usually results from too long continued use of medicinal doses. Chloral has been used as "knock-out drops" for the purpose of effecting robbery³ and rape. In most cases of poisoning the drug has been taken by the mouth, but death has resulted from its introduction into the rectum and from its injection into a vein for the purpose of producing surgical anesthesia. Chloral passes to the fetus and may cause the death of this without killing the mother.⁴

Death has been reported from bromidia, a proprietary preparation now said to contain about 12 grains of chloral in a fluidram.⁵

Properties.—Pure chloral (CCl_3CHO) is an oily liquid and is seldom seen. It gives all the reactions of aldehyds, and is oxidized by nitric acid to trichloroacetic acid. Chloral hydrate (Chloralum hydratum, hydrated chloral, U. S. P., $\text{CCl}_3\text{CHO}\cdot\text{H}_2\text{O}$) is formed by mixing chloral with water; it occurs in the form of granular, sugar-like crystals. It is slightly volatile at ordinary temperatures, melts at about 58°C . (136.4°F .), and boils at 97.5°C . (207.5°F .). It is easily soluble in water and alcohol. It has a peculiar odor, often compared to that of a melon and a disagreeable taste; the latter is almost absent when the drug is dissolved in alcoholic beverages. Chloral is rapidly decomposed by alkalis into chloroform, formates, and water, at ordinary temperatures.

Physiologic Action.—The action of chloral is essentially the same as that of alcohol and chloroform—*i. e.*, it depresses and eventually paralyzes the central nervous system. There is seldom, however, a period of excitement with chloral, and the sensation of pain is not greatly dulled until very large doses have been administered. The chief effect of small doses is to cause sleep that closely resembles natural sleep. With larger doses the sleep is more profound and the patient can no longer be aroused to complete consciousness; the reflexes are lessened, the respiration and heart are slowed, and the blood-pressure is lowered. With very large doses the effect is almost exactly similar to that observed in the third stage of anesthesia from chloroform; reflexes and sensation are completely abolished and the muscles are

¹ This substance is usually termed chloral; and by "chloral" in this article is meant chloral hydrate, unless the contrary is stated.

² Witthaus, *Manual of Toxicology*, 1911, 1176.

³ Case 4; see also Bancroft Case, *Pharm. Jour.*, 1908, 27, 669.

⁴ Jung, *Therap. Monatsh.*, 1914, 28, 104.

⁵ Report of Council of Pharmacy and Chemistry, *Jour. Amer. Med. Assoc.*, 1914, 62, 1573, see Wood, *Ibid.*, 1906, 46, 1220; also, Bennett, *Ibid.*, 1922, 79, 1048.

relaxed. The prolonged administration of chloral leads to fatty degeneration of various organs. Locally, chloral is an irritant; it also possesses antiseptic properties. Chloral is excreted in the urine in combination with glycuronic acid; this compound reduces Fehling's solution, and so may be mistaken for sugar. Chloral is not decomposed by the blood into chloroform.

Symptoms.—The symptoms of chloral poisoning vary widely in different cases. In some cases, especially in conditions of weakened heart action, as in delirium tremens, the insomnia of continued fevers, etc., death may result very rapidly from failure of the heart¹; in some cases it occurs even before drowsiness is noticed. In a few cases there is a period of excitement² and the individual may act like an intoxicated person. There may be nausea and vomiting, due to the local action of the drug upon the stomach. In most cases the patient falls into a deep sleep from which it is impossible to arouse him; the pulse is scarcely perceptible; the respiration is irregular and shallow; the pupils are moderately contracted, rarely dilated; the face is cyanotic or, in the earlier stages, flushed, on account of the dilatation of the vessels; the extremities are cold. There is usually a fall of temperature from the beginning: it may sink to 86° F. In rare cases a rise of temperature has been noted.³ Death usually occurs in coma and seems to be due, as a rule, to failure of the respiration; sometimes it is due to pulmonary edema. Occasionally convulsions and delirium occur. The patient may apparently recover, but die later, or various symptoms may continue for some time.⁴

The symptoms of chronic chloral poisoning are various, and the condition is often difficult to diagnose. There are frequently disturbances of digestion, with diarrhea and loss of weight. Affections of the skin are common; these may take the form of a scarlatina-like rash, of vesicles, or of a superficial ulceration at the roots of the nails. There is frequently much irritation of the eyes, as shown by itching, redness, swelling, and excessive secretion. These symptoms may follow a single large dose or a number of small ones. The nervous symptoms are marked: sleeplessness, indefinite pains, general depression with impairment of the mental faculties are often observed. In some cases a condition resembling melancholia results, while in others it is difficult to distinguish the condition from parietic dementia.⁵ Sudden withdrawal of the drug sometimes leads to symptoms resembling the delirium tremens caused by alcohol. Sudden death is common among habitual chloral takers; it seems to be due to failure of the heart, and may occur after doses but slightly larger than those to which the patient is accustomed.

¹ Case 1.

² Case 2.

³ Plummer, *Lancet*, 1894, i, 21; also Case 3. Possibly the large doses of strychnin administered in some of these cases contributed to the elevation of the temperature, but usually some rise was noted before the strychnin was injected.

⁴ Rogers, *Medical Record*, 1900, lvii, 412 (recovery from 680 grains—44 gm.—taken in three days); see also Case 3.

⁵ Case 5.

Fatal Dose.—The fatal dose of chloral seems to be dependent to a considerable degree upon the age and condition of the individual. Children have been said to bear chloral better, in proportion, than do adults, but 3 grains (0.194 gm.) have been fatal to an infant a year old and 46 grains (2.98 gm.) to a child of five years. Although much larger doses are frequently given and may be necessary in cases of tetanus and in some other conditions, 30 (1.94 gm.) and even 20 grains (1.29 gm.)¹ have on numerous occasions caused the death of adults. A patient suffering from epileptic mania recovered from 1.1 ounces (34.2 gm.), and in a case of tetanus 3 ounces (93.3 gm.) were given in twenty-four hours without causing death.² Recovery has sometimes followed the taking of 1 ounce (31 gm.)³ or more of chloral. Recovery has frequently followed the taking of from 160 to 180 grains (10.36 to 11.66 gm.); after such large doses the recovery has doubtlessly been due in many cases to the prompt treatment; 120 grains (7.77 gm.) would probably be very dangerous to most adults in good health, and 150 grains (9.71 gm.) fatal⁴; much smaller quantities would be fatal to most aged individuals and to those having a weak heart. Professor Tyndall died from the effects of taking 80 grains (5.18 gm.).

Fatal Period.—The fatal period is variable, and seems to be partly dependent upon the size of the dose; 30 grains (1.94 gm.) caused death in thirty-five hours⁵; doses of 75 grains (4.85 gm.) have caused death in from fifteen minutes to one hour. Perhaps in most of the recorded cases death has occurred in from six to ten hours. Yet death has taken place within ten minutes after taking from 20 to 30 grains (1.29 to 1.94 gm.). In several of the very rapidly fatal cases there has been disease or weakness of the heart. In a number of cases death has occurred suddenly after the last of several small doses.

Treatment.—The stomach should be washed out with warm water; emetics often fail to cause vomiting on account of the great depression of the nervous system. If, for any reason, it is not possible to wash out the stomach, the administration of an alkali may be of use; some of the chloral may be destroyed in this manner.⁶ Chloral is absorbed so rapidly that in many cases probably little or none of the drug is in the stomach when the patient is seen by the physician; hence physiologic antidotes are necessary. Of these, strychnin hypodermically and drafts or rectal injections of hot coffee seem to give the best results. Atropin and camphor are also recommended. Artificial respiration is sometimes necessary. The temperature of the patient should be maintained by the use of blankets, hot-water bottles, etc.

In chronic chloral poisoning the drug should be rapidly withdrawn, and stimulants, such as strychnin and digitalis, given. Special atten-

¹ Case 1.

² Editorial, Practitioner, 1877, xix, 116.

³ Case 3.

⁴ Blyth, Poisons, 4th ed., 1906, 165.

⁵ Case 2.

⁶ Dougall, Glasgow Med. Jour., 1895, xliii, 95.

tion should be paid to the diet. In many cases the treatment is successful only in special hospitals.

Postmortem Appearances.—No characteristic lesions are caused by chloral. The brain is said to be, as a rule, hyperemic, and the blood to be dark and fluid. The mucous membrane of the throat, esophagus, and stomach may be reddened and inflamed. The contents of the stomach may have the odor of chloral. Occasionally there is edema of the lungs. In chronic cases of chloral poisoning fatty degeneration of the heart is common; fatty degeneration or fatty infiltration of the kidneys has been produced experimentally in animals by the administration of chloral.

CASES OF POISONING BY CHLORAL HYDRATE

CASE 1.—Woman, aged thirty-three, wished to have teeth extracted and was given 10 grains (0.65 gm.) of chloral to prevent pain. A second dose of 10 grains (0.65 gm.) was given one hour later; in a few minutes symptoms of poisoning appeared and death occurred in about fifteen minutes.¹

CASE 2.—Woman, aged twenty, given at 10 p. m. 30 grains (1.95 gm.) of chloral for sleeplessness. Caused pain and burning in chest and some excitement. In the morning was found very pale and unconscious; could not be aroused. Labored respiration; no pulse at wrist; extremities were cold; pupils dilated. This condition continued practically unchanged, notwithstanding that various stimulants were administered, until death occurred about thirty-five hours after the dose was given. There was at no time any return of consciousness or any movements.²

CASE 3.—Woman in excellent health, aged thirty-four, took at 8 a. m. 1 ounce (31 gm.) of chloral dissolved in 2 ounces (59.2 c.c.) of water. At 4 p. m. she was discovered in bed unconscious, and it was impossible to arouse her. When seen by physician at 5.30 p. m. she was comatose and all reflexes were abolished. Respiration shallow and stertorous; pupils small and sluggish; pulse 130; temperature 100.5° F. Atropin and later strychnin and ether were given hypodermically. The stomach was washed out with difficulty. Nitrite of amyl by inhalation improved the pulse. Enemata of strong coffee were given at 10 p. m.; sinapisms were applied to legs, and patient was vigorously rubbed with towels. At midnight the temperature was 103° F., pulse was flagging, and the prognosis was grave. Enemata of coffee, milk, and brandy and hypodermic injections of strychnin were continued. At 12.30 a. m. she showed the first signs of animation—twitchings of face, movements of limbs, and soon groaning and restlessness. Imperfect consciousness soon returned, but patient slept most of the day. Nine-tenths grain (0.06 gm.) of strychnin had been given. The temperature did not fall for a day or two. Patient did not leave room for over three weeks, and for some time afterward there was impairment of digestion and muscular tone, and periods of excitement alternated with periods of great depression for six weeks.³

CASE 4 (The "Manchester Cab Mystery.")—J. F., a man weighing about 15 stones (210 pounds), had been drinking during the day and by evening was partially intoxicated. At 6.20 he drove to a public house with a young man and had a glass of beer. Re-entered the cab at 7.10. He is said to have walked quite steadily and seemed to be sober. At about 7.25 cabman found the cab-door open. J. F. was alone, his head had fallen forward on to the front seat, he was unconscious but could be roused, and could just speak. All his valuables were gone. He died at 8.05, death being due immediately to syncope. Autopsy nineteen hours after death. Organs had a strong odor of alcohol. Heart showed slight fatty degeneration. Stomach slightly congested. Liver large, fatty, and cirrhotic. Traces of chloral were found in the contents of the stomach and upper part of the small intestine. It was proved that the young man who had accompanied J. F. had twice used chloral for drugging persons, and that he had put something into one of the glasses of beer at the public house. He was convicted of murder in the first degree.⁴

¹ Ingals, *Chicago Med. Jour. and Exam.*, 1877, xxxiv, 234.

² Fuller, *Lancet*, 1871, i, 403.

³ Colenso, *Lancet*, 1894, ii, 1034.

⁴ Reynolds, *Brit. Med. Jour.*, 1889, ii, 235.

CASE 5.—Lady, aged fifty-six, had been ill for five years. For a year and a half had been taking a proprietary medicine containing chloral; recently the dose had been increased, but the total amount did not exceed 20 grains (1.29 gm.) of chloral a day. She had delusions, transitory in character and of a grandiose form. Ataxia, especially of the lower limbs, was marked. General tremor was present, pupils were unequal, and speech was tremulous. There was marked insomnia. Had been violent at times and had delusions of persecution. Diagnosis of parietic dementia was made, and patient was about to be sent to an insane asylum. All hypnotics, however, were withdrawn, and in a few days her delusions began to wane and her nervous state to improve. Tremors lessened, speech sharpened, and the pupils reacted equally. Six weeks after the withdrawal of the chloral she went home and resumed the management of her estate.¹

H. H. Kane² gives a summary of 63 cases of poisoning by chloral; the symptoms, fatal dose, etc., are fully discussed.

Isolation.—In dealing with organic matter supposed to contain chloral one must bear constantly in mind that this substance is decomposed by caustic alkalis, giving rise to chloroform and a formate; but as very dilute alkalis are inefficient in effecting this decomposition, chloral may be recovered from a fluid that is initially faintly alkaline.³ In such a case the material should be acidified with tartaric acid as soon as possible.

The method of distillation with steam described under alcohol is peculiarly useful for the isolation of chloral, since by the ordinary method it is necessary to evaporate, almost to dryness, in order to obtain the greater portion of the poison. To the dilute aqueous distillate the following tests may be applied.⁴

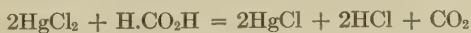
Tests.—1. To a rather large amount of the distillate is added some magnesium oxid, and the fluid is boiled in a flask provided with a long condensing tube:



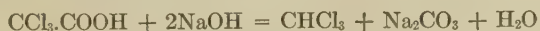
After heating on the water-bath to expel the chloroform, the liquid is made acid with tartaric acid, and the formic acid is distilled off and identified by appropriate tests.

(a) On boiling a solution of formic acid with acidified potassium permanganate, the latter is reduced and the color of the solution disappears.

(b) When heated with a solution of mercuric chlorid, formic acid causes the formation of insoluble mercurous chlorid.



Trichloroacetic acid also yields chloroform when treated with alkalis, but no formic acid is produced⁵:



¹ Coe, Quarterly Journal of Inebriety, 1899, xxi, 65.

² Medical Record, 1880, xviii, 702; 1881, xix, 4, 32, 60, 284, 310, 460, and 482.

³ Chloral hydrate is decomposed instantly by normal caustic soda in the cold, but by tenth-normal alkali only slowly in the warm. Meyer and Haffter (Ber. d. d. chem. Ges., 1873, 6, 600).

⁴ The various methods of extraction which have been recommended for chloral involve great loss of material and are inferior in every way to the one described.

⁵ Beckurts and Otto, Ber. d. d. chem. Ges., xiv, 589; Seubert, *ibid.*, xviii, 3342.

2. Phloroglucin and sodium carbonate with chloral, standing at room temperature for about one-half hour gradually develops lilac to orange, to blood-orange, to deep red color. If extremely small quantities of chloral are present, the color develops to orange only, and if as low as .01 mg. in 1 c.c. is present, the color is a cross between orange and the light violet of the reagents themselves. Even in this extremely dilute solution a positive reaction may easily be recognized if compared with the control. Chloroform does not give this reaction. The color obtained with chloroform on the other hand is the slight violet of the reagents themselves. Formaldehyd and acetaldehyd interfere in that they give a reddish color. If the absence of aldehyd is shown by the reduced fuchsin test (which is not given by chloral), then the phloroglucin test may be looked upon as a sensitive method for purposes of differentiation. The technic is as follows:

To 1 c.c. of distillate add 4 drops of saturated phloroglucin solution and 1 c.c. of 20 per cent. sodium carbonate and allow to stand. Gradually the color develops, lilac to orange, to blood-orange, to deep red (sensitiveness, 0.01 mg. in 1 c.c.).¹

3. Resorcin with sodium hydroxid and boiling have been used for a long time. Some workers, notably Schwartz,² the originator of the test, claim that besides the red color there is a green fluorescence given by both; others, notably Witthaus,³ claim that only chloral gives the fluorescence. With the use of resorcin and sodium carbonate, and at room temperature for one-half hour one of us (Gettler) finds, first, that with chloroform a green fluorescence never appears, and that with chloral, even in minute amounts, fluorescence always occurs; second, that although the red color does not appear in very dilute solutions of chloral, the green fluorescence, especially if the reaction product is diluted with 10 c.c. of water, is always present; third, its sensitiveness is 0.1 mg. in 1 c.c.; fourth, formaldehyd, acetaldehyd, formic acid, benzaldehyd, that is, substances of an aldehyd character, do not give the reaction; fifth, if formaldehyd is present together with the chloral the reaction is not interfered with, provided the test is done at room temperature. The technic follows:

To 1 c.c. of distillate are added 6 drops of saturated resorcin solution and 1 c.c. of saturated sodium carbonate, or less if only traces of chloral are present. Let stand for one-half hour, then dilute by adding 10 c.c. of water. A beautiful green fluorescence results if chloral is present. Chloroform will not give this reaction. In cases of extremely small quantities of chloral, viewing by direct sunlight against a black, glossy background is of great advantage. Any development of color or fluorescence after many hours is of no consequence.⁴

4. Many of the tests for chloroform (which see) are also given by chloral.

¹ Gettler, A. O., *Proc. Soc. Exp. Biol. and Med.*, 1919, xvi, 110-116.

² *Ztschr. f. Anal. Chem.*, 1888, 27, 668.

³ *Text-book of Medical Jurisprudence and Toxicology*, 4, 1171.

⁴ Gettler, A. O., *Loc. cit.*

Estimation.—The amount of chloral hydrate present in an aqueous solution can easily be determined. The liquid is shaken with magnesium oxid to remove any free acid, and treated with an excess of standard sodium hydroxid (must be as strong as a normal solution). After the excess of alkali has been determined with a standard acid, the amount of chloral hydrate can be found by an obvious calculation. Minus 1 c.c. of normal alkali corresponds to 0.1655 gram of chloral hydrate.

Urochloral Acid ($C_8H_{11}Cl_3O_7$).—**Properties.**—Found in urine, if chloral has been taken. It crystallizes in needles, melting point $142^\circ C.$ ($287.6^\circ F.$), soluble in water, alcohol, and ether. It reduces Fehling's solution. It rotates polarized light to the left. If hydrolyzed by dilute acid, it yields trichlorethyl alcohol and glycuronic acid.

Isolation.—Evaporate the urine on a water-bath to a syrupy consistence. Acidify strongly with sulphuric acid. Shake out several times in a separatory funnel with an alcohol-ether mixture (1:3). Separate this alcohol-ether layer and evaporate it, leaving the aqueous acid residue. This is neutralized with KOH and evaporated. The dry residue is taken up with 90 per cent. alcohol, filtered, and the filtrate precipitated with ether. This precipitate is filtered off and washed with ether and absolute alcohol. The precipitate is further boiled with absolute alcohol and filtered hot. On cooling, the potassium salt of urochloral acid separates in the form of tufts of silky needles. To purify further, these crystals are filtered off, again washed with absolute alcohol and ether, again boiled up in absolute alcohol, filtered hot, and allowed to crystallize.

If the free acid is preferred, the potassium salt is dissolved in a little water and acidified with HCl. This solution is shaken out with an ether-alcohol mixture (8:1). The double solvent is distilled off and the residue treated with moist silver oxid until no more chlorid precipitates. The silver chlorid is filtered off. In the filtrate the soluble silver salt is decomposed by H_2S and the filtrate is carefully evaporated to a syrup. After a few hours needle-shaped crystals in clusters of stars develop.¹

Tests.—1. Crystalline form and melting point.

2. Hydrolyzing with HCl yields glycuronic acid and trichlorethyl alcohol. Therefore, on distilling with acid, the above substances are produced. At the same time glycuronic acid with the HCl yields furfurol, which distills over. If a drop of this distillate is brought in contact with a drop of anilin acetate on a filter paper, a red color is produced. It must be remembered that a faint reaction may be due to small amounts of pentoses and pentosans in urine.

CHLOROFORM

Most of the deaths from chloroform result from its use as an anesthetic in surgical practice. In various compilations of statistics the death rate in anesthesia from chloroform has varied from 1 in 1000

¹J. von Merinz and Musculus, Ber. d. d. Deutsche chem. Ges., 1875, viii, 662, and 1882, xv, 1020.

to 1 in 5900; 1 in 3500 is considered a fair average. Chloroform is occasionally used either by inhalation or more frequently taken internally as a means of committing suicide; there were 8 fatal cases from this use in St. Louis in 1910 to 1914. Occasionally chloroform liniment or chloroform is taken internally by mistake or an overdose is taken. Occasionally a death results from its use as an anthelmintic. It is occasionally used as an intoxicant, being taken either internally or inhaled. Chloroform is rarely used for the purpose of murder; in the reported cases it has usually been administered by force. It is possible in animal experiments to cause sudden death by the inhalation of concentrated chloroform vapor by reflex stoppage of or by a direct toxic action on the heart; this may have occurred in a few criminal cases. By proceeding very cautiously it is possible to chloroform a person while asleep,¹ but, as a rule, the person awakes before anesthesia begins; there seem to be no authentic cases of the use of chloroform in this manner for criminal purposes.

Properties.—Chloroform (Chloroformum, U. S. P., trichlormethane, CHCl_3) is a heavy, colorless liquid of a characteristic ethereal odor, a burning, sweet taste, and a neutral reaction. Soluble in something over 200 parts of water; mixes in all proportions with ether and with alcohol. Specific gravity, 1.491; boiling point, 62°C . (143.6°F). Crude, unpurified chloroform, from which fatal poisoning taken by mouth has been reported,² contains hydrochloric acid, free chlorine, various chlorinated products other than chloroform, and phosgene. Chloroform and its vapors are not inflammable, but when it is used for a long time, as in obstetric or surgical cases, near a flame, there are formed decomposition products—phosgene (carbonylchlorid, COCl_2), chlorine, and hydrochloric acid—which are very poisonous; fatal poisoning has resulted from the action of these products.³ The addition of alcohol and keeping it in the dark prevents such decomposition. On warming with alcoholic potash it is decomposed into potassium chlorid and formate while on heating with alcoholic potash and ammonia it yields potassium cyanid.

Physiologic Action.—Locally, chloroform is an irritant; hence its use as a liniment. If liquid chloroform comes into contact with the skin and evaporation prevented, as under the edge of a mask, blisters may result; these have served as a basis for suits against physicians. Taken by the mouth it causes pain, vomiting, and frequently diarrhea. When inhaled—the usual method of administration—the local action of the vapor upon the mucous membranes of the air-passages is often very marked and consists of a reflex slowing or stoppage of the respira-

¹ Kelly, *Med. Rec.*, 1890, 37, 352; see also Editorial, *Therap. Gaz.*, 1894, 18, 758; Editorial, *Med. Rec.*, 1890, 37, 42; Coleman, *Ibid.*, 139.

² Schelcher, *Viertelj. ger. Med.*, 1920, 60, 175.

³ See Gerlinger, *Arch. f. exper. Path. u. Pharm.*, 1902, 47, 428; Betagh, *Brit. Med. Jour.*, 1905, i, *Epit. Cur Lit.*, 63; Armand and Bertier, *Rev. de Chir.*, 1905, 32, 37; Achard, Leblanc and Binet, *Arch. de méd. exp.*, 1920, 28, 628; Wiki, *Rev. Méd. de la Suisse Rom.*, 1921, xli, 38; Laqueur and Magnus, *Ztschr. f. exp. med.*, 1921, 13, 31, and 200; Hertzmann, *Ibid.*, 180.

tion, a reflex rise of blood-pressure, and a slowing of the heart; these reflex effects are usually of but brief duration.

When chloroform reaches the circulation, the effects are similar to those of ether. There is a period of excitement, due either to a stimulation of certain parts of the central nervous system or, more probably, to a paralysis of certain controlling centers. After the period of real or apparent stimulation, which is usually brief, comes a stage of depression; the higher centers of the brain are first affected, then the spinal cord, and last of all the medulla. The sensory functions of the brain and cord are depressed earlier than are the motor. Respiration becomes slow from the depression of the respiratory center, the heart beats more weakly from a direct action of the poison on the cardiac muscle, and the blood-pressure sinks. The temperature falls during even a short period of anesthesia. Fatty degeneration of the liver, heart, and kidneys follows the repeated administration of chloroform or sometimes a single prolonged administration.¹ Chloroform is eliminated almost exclusively by the lungs.

Symptoms.—It is customary to recognize three stages in the symptoms produced by chloroform. The first stage is that of excitement. There is a feeling of warmth—first of the face, then of the entire body—followed by a tingling sensation of the skin. There are ringing and roaring sounds in the ears, and vision becomes distorted. Consciousness is soon lost, and the patient may struggle violently and indulge in profane or abusive language. The second stage is that of surgical anesthesia; the muscles are relaxed, the patient lies perfectly still with regular but rather slow and shallow respiration, and is entirely insensible to pain. This stage may be maintained for hours. If the inhalation of chloroform be discontinued at this stage, the patient usually awakes within from twenty to forty minutes, but he may not awake for some hours. Vomiting, which may occur at almost any stage, may persist for some time. There is usually some confusion of ideas also. The third stage is that of paralysis, and is characterized by a fall of blood-pressure and the failure of the respiration and heart. The skin becomes dark and cyanotic, and the pupils dilate widely. There has been a discussion in progress for many years as to the cause of death in chloroform inhalation; some maintain that it is due to failure of the heart, others to failure of the respiration. It seems probable that in most cases in which death occurs late in the anesthesia the respiration ceases first; in many cases life may be maintained for some time by means of artificial respiration, the heart continuing to beat fairly well. In other cases the heart is so deeply poisoned that it is unable to beat long after the respiration has ceased, although artificial respiration is maintained; this occurs most frequently when the chloroform vapor is inhaled in concentrated form.

Very many of the deaths from chloroform have occurred early

¹ Fränkel, Virchow's Archiv. 1892, 127, 381; Strassmann, Berlin. Klinik, Feb. 1, 1898, x-xi (Heft 116), 1; Whipple, Jour. exp. med., 1912, 15, 246; Marshall and Rowntree, Ibid., 1915, 22, 333.

in the anesthesia,¹ at the very beginning of the operation or even before the operation was commenced,² or when the patient had been allowed partially to come out and chloroform was again administered.³ In most of these cases of sudden death the heart stopped suddenly and before the respiration. This form of death has been attributed to a sudden overloading of the heart with concentrated chloroform vapor, and Pohl⁴ found that dogs could be killed in this way and that the blood in the left side of the heart might contain ten times as much chloroform as that in the right side. A lethal amount of chloroform may be absorbed from a few deep inhalations. Embley⁵ has adduced a number of experiments and arguments to show that overactivity of the vagus nerves leading to permanent stoppage of the poisoned heart may be responsible for this form of death, and states that in dogs it may be prevented by section of the vagi or by their paralysis with atropin. Levy,⁶ on the other hand, believes that in these cases there is a condition of very light anesthesia during which the heart is easily thrown into ventricular fibrillation with immediate death. He states that this form of death does not occur during deep anesthesia. The fibrillation is especially likely to occur from sensory nerve stimulation; reflexes through the accelerator nerves or an increased secretion of the adrenal glands may be a factor, for it was found that the injection of epinephrin into animals in light chloroform anesthesia would cause ventricular fibrillation. Whatever the explanation of this form of death, it is recognized that it is dangerous to operate under imperfect chloroform anesthesia.

The condition of the patient is also frequently a factor in the fatal result. It is dangerous to administer chloroform to the very old, to those suffering from fatty heart, atheromatous arteries, diabetes, chronic diseases of the kidneys, or in status lymphaticus. Many fatalities occur among drunkards; it has been stated that the mortality among these has been as high as from 10 to 13 per cent. Death occasionally results from suffocation due to the drawing into the air-passages of vomited matter.

Death occasionally occurs under chloroform when every precaution is taken; as such cases occurred in operations before the introduction of anesthetics, it seems very probable that sometimes death is not due to the anesthetic at all.⁷

Delayed chloroform poisoning or postanesthetic toxemia⁸ may develop after apparent recovery from the anesthetic; this is especially likely to occur when the anesthesia has been prolonged or when

¹ For long lists of such cases see J. C. Warren, *Chloroform and Chloric Ether*, 1849; Levy, *Proc. Roy. Soc. Med.*, 1914, 7, Sect. on Anesthet., 57.

² Case 2.

³ Case 3.

⁴ Pohl, *Arch. exp. Path. u. Therap.*, 1891, 28, 239.

⁵ Embley, *Brit. Med. Jour.*, 1902, i, 817, 885, 951, 975.

⁶ Levy, *Loc. cit.*; Heart, 1913, 4, 319; 1914, 5, 299.

⁷ See Case 2.

⁸ Favill and Bevan, *Jour. Amer. Med. Assoc.*, 1905, 45, 691; Stiles, *Ibid.*, 1912, 58, 434; Renton, *Brit. Med. Jour.*, 1907, i, 617.

it has been repeated, even for short periods, within a few days.¹ Diabetes, hepatic disorders,² acetonuria, wasting diseases, etc., predispose to it; it is especially frequent in children.

The symptoms, which generally develop within twenty-four to forty-eight hours, but may occur in ten hours or be delayed for three or four days, are referable to severe damage to the liver, heart, or kidneys. The patient becomes restless, and vomits repeatedly; jaundice, tenderness over the liver, delirium, and coma appear; there may be cutaneous hemorrhages. The blood shows retention of non-protein nitrogen, urea, and amino acids as in phosphorus poisoning.

The symptoms following the taking of chloroform internally are due partly to the local irritant action, partly to the effects after absorption. The local irritant action of the poison leads to intense pain in the throat and abdomen, and the patient may throw himself about violently. Vomiting usually results, and there is sometimes involuntary evacuation of the bowels. The chloroform is rapidly absorbed, and the subsequent symptoms may resemble those caused by the inhalation of the drug. With small doses there may be a period of excitement and the patients stagger like a drunkard; with large doses the depression begins at once. In most of the recorded cases unconsciousness seems to have come on within ten minutes. The skin becomes cyanotic and cool, the respiration irregular and stertorous, and the breath smells of chloroform; the pulse is small and weak; the pupils may be dilated or contracted, or pass rapidly from the one state to the other; vomiting soon ceases, owing to the depression of the nerve-centers; with most "irritant" poisons it is very persistent. Death may occur in coma, but it seems due in many cases to gastritis. Coma may continue for many hours and recovery still take place, but abdominal pain, bloody diarrhea, swelling of the liver, jaundice, and painful micturition may continue for several days. Death may occur after some time from pulmonary edema, failure of the heart, or, more frequently, from gastritis. The death-rate in cases in which chloroform has been swallowed is high. In a series of 57 cases collected by Eliot,³ 15 died, while of 17 cases reported by Hirsch,⁴ 7 died. Thus the death-rate has been from 26 to 41 per cent.

There is also a chronic form of chloroform poisoning due to the individual inhaling⁵ or drinking the drug; this habit is frequently the result of the use of small amounts for the relief of pain, and is sometimes associated with other drug habits. The chief symptoms are due to disturbances of the digestive and nervous systems. The patient may have hallucinations or pass into a condition that cannot be distinguished from the delirium tremens of alcoholism.

Fatal Dose.—It is impossible to make any definite statements as to the fatal dose of chloroform when taken by inhalation; it is far more a question of the concentration of the vapor than of the absolute amount

¹ Case 5.

² Compare Weber, *Internat. Clinics*, 1920, 4, 54.

³ Eliot, *Medical Record*, 1885, xxvii, 29.

⁴ Hirsch, *Zeitschr. f. klin. Med.*, 1894, xxiv, 190.

⁵ Storath, *Deut. med. Woch.*, 1910, 36, 1362; Friedländer, *Ibid.*, 1907, 33, 1494.

inhaled. Air containing 1.5 per cent. of chloroform causes death in animals in one-half hour, and since Geppert¹ has shown that it requires the same concentration of chloroform vapor to anesthetize the lower animals as man, this concentration would doubtless soon be fatal to man; hence the rule is frequently laid down that patients should not even for a short time, receive air containing more than 3.5 per cent. of chloroform vapor. Cases have been reported in which 30, and even 15 drops of chloroform have caused death; on the other hand, 22½ ounces (997 gm.) have been inhaled in twenty-four and even in twelve hours, and the patient recovered. The fatal dose of chloroform when taken per os is also difficult to determine. A child of four years died from 1 dram (5.6 gm.), while another of the same age recovered from nearly twice as much. An adult died from about 15 gm., while others recovered from 70² and 222 gm.³ Forty minims (3.7 gm.) have caused severe, but not fatal, poisoning.⁴ In most of the recorded fatal cases from ½ to 2 ounces (22.5–88.5 gm.) of chloroform have been taken; as a rule, death will almost certainly follow the administration of 11 or 12 drams (61.5 or 67.5 gm.)

Fatal Period.—Death may occur at any stage of chloroform inhalation. In about one-half of the reported cases death has occurred before anesthesia was fully produced—*i. e.*, within ten or fifteen minutes.⁵ In cases of “delayed poisoning” death usually occurs in four to five days.⁶ When chloroform is taken internally, death may occur within an hour or it may be delayed for several days; in 2 cases it occurred eight days after the chloroform was taken. In most of the recorded cases death has occurred after the first twenty-four hours.

Treatment.—In case of the failure of the respiration during the inhalation of chloroform the administration of the anesthetic should be immediately stopped. The head should be lowered and the feet raised so as to drive the blood to the brain. Artificial respiration should be commenced. If the heart is weak, rhythmic pressure over the heart may be practised. Cardiac massage, most effectively practised by opening the abdominal cavity, inserting one hand below the diaphragm, and compressing the heart between this hand and the other hand on the chest wall, has been successful.⁷ Injection of epinephrin into the pericardial sac has apparently saved life in cases in which the heart has failed as the result of a long-continued anesthesia. According to Levy's views and animal experiments this treatment would be contraindicated in conditions of sudden stoppage of the heart during light anesthesia. Embley found that in dogs the sudden stoppage of the heart could be

¹ Geppert, Deut. med. Woch., 1899, 25, 447.

² Shoemaker, Mo. Cyclo. and Med. Bull., 1908, i, 501.

³ See Case 4.

⁴ Marshall, Medical News, 1898, 73, 654.

⁵ See, *e. g.*, Brouardel, Bull. de l'Acad. de Med., Feb., 1902, 47, 226. According to Embley (*loc. cit.*), of 83 cases of death which occurred in England during 1899, 68 happened before the operation was started; in another year it was 39 out of 41.

⁶ Herb, Jour. Amer. Med. Assoc., 1911, 56, 1312.

⁷ Jurasz, Münch. Med. Woch., 1911, 58, 83 (earlier literature); Mollison, Proc. Roy. Soc. Med., 1916, 10, Sect. on Anest., 1.

prevented by the injection of atropin; in case of sudden stoppage the intracardial injection of this drug might prove of value. It is doubtful whether the numerous other drugs which have been recommended are of value. The treatment when the chloroform has been taken internally is that of an irritant and narcotic poison. The stomach should be washed out with warm water or milk; emetics may be used, but they are somewhat uncertain in their action in these cases, owing to the depression of the medulla. Much relief is obtained from the use of demulcent drinks, such as olive oil. Strychnin, digitalis, atropin, ammonia, hot coffee, etc., may be used as stimulants; cold affusions and, in extreme cases, artificial respiration should be resorted to. If the patient recovers from the coma, the gastritis should receive appropriate treatment.

Postmortem Appearance.—When death has resulted from the inhalation of chloroform, no characteristic changes are found. Congestion of the lungs, bronchi, and kidneys has been described. The organs occasionally have the odor of chloroform. In cases of poisoning by liquid chloroform there are usually redness of the mucous membrane of the stomach and throat, and sometimes ulceration. The epithelium of the pharynx, glottis, and gullet may be softened and easily detached. If death has occurred in a short time, chloroform is found in the stomach; the contents of the stomach may have the odor of the poison. If death has been delayed¹ for a few days, jaundice and fatty degeneration of the heart, liver, and other organs may be found; the latter has been observed also after prolonged narcosis and in cases of chronic poisoning.

CASES OF POISONING BY CHLOROFORM

Eliot gives a summary of 57 cases of chloroform poisoning in which the drug was taken internally²; Hirsch gives a summary of 17 such cases.³

CASE 1.—Man, aged forty-three, swallowed at 7 A. M., after a sleepless night, about 1 ounce (45 gm.) of chloroform to secure sleep. When seen at 10.15 he was dazed, but on being roused could answer questions intelligently; breath smelt of chloroform. Complained of severe pain in umbilical region; constant desire to defecate and much straining. Had vomited once. Tongue and back of throat red and very sore. Fell asleep for a few minutes at a time; was awakened by pain. Pulse 120; respiration 56. At 12.20 P. M. began to pass blood from bowels; vomiting became frequent, and the vomited matter was blood-stained. No urine had been passed, although frequent painful attempts had been made; catheterized; urine was blood-stained. The patient remained awake and suffered intense pain; grew worse and died about 7.30 P. M., about twelve hours after taking the poison. No autopsy.⁴

CASE 2.—Patient [very anemic; dreaded chloroform. Twenty or 30 drops given on lint, but before he was nearly under the influence and only a few seconds after he had been talking it was noticed that the breathing had become shallow; the pulse was fair and the reflexes were present. Conditions rapidly became dangerous; efforts to revive him failed. Patient was at no time under the influence of the anesthetic, and death was attributed to syncope caused by fear.⁵

CASE 3.—Child, aged five, anesthetized with "A. C. E. [alcohol, chloroform, and ether] mixture," anesthesia being continued by chloroform alone. Tonsils removed; pulse and respiration good. Signs of "coming round," so a little more chloroform was given preparatory to the removal of adenoids.⁶ "She had hardly taken one

¹ Case 5.

² Medical Record, 1885, xxvii, 29.

³ Zeitschr. f. klin. Med., 1894, xxiv, 190.

⁴ Bridgman, Lancet, 1897, ii, 384.

⁵ Editorial, Ibid., 1891, ii, 1117.

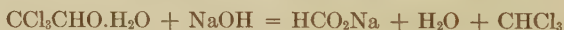
⁶ Death from chloroform seems to be especially frequent during operations for the removal of nasopharyngeal adenoids.

or even two shallow breaths when her eyes suddenly became fixed, respiration ceased, and the pulse stopped." Child was inverted and artificial respiration maintained for twenty-five minutes, during which time there were two spasmodic gasps at an interval of a few minutes. Two drams (7.5 c.c.) of A. C. E. and 1 dram (3.7 c.c.) of chloroform had been used; much of latter had been wasted. Autopsy negative.¹

CASE 4.—Man, aged forty-six, drank 5 ounces (222 gm.) of chloroform with suicidal intent—time not stated; vomited soon afterward. When brought to hospital seemed almost dead; no respiratory effort was visible, and the pulse could be felt only with difficulty. Face pale; lips cyanotic. Pupils widely dilated. Corneal reflex absent. After a few minutes of artificial respiration patient began to breathe. Stomach washed out; contents had no odor of chloroform, but the expired air did. Strychnin injected. Consciousness returned four hours after beginning of treatment. Complained of pain in mouth and abdomen. On the following day a scarlatiniform eruption on arms and legs. Left hospital after two days apparently entirely well.²

CASE 5.—Man, twenty-nine, operated on under chloroform for stab wound in cheek; operation lasted twenty minutes. Two days later slight jaundice; next day drowsiness, increasing to stupor; 2 convulsive attacks on third day. On third day patient more or less comatose; exploratory trephining of skull, under chloroform, forty-five minutes. Patient remained comatose; the jaundice gradually increased; death on the fifth day after the first chloroforming. Postmortem, the typical macroscopic appearance of acute parenchymatous atrophy "as if the capsule was too large for the amount of hepatic glandular tissue which it contained." Microscopically there was more or less degeneration or atrophy of nearly all the liver cells.³

Isolation.—The isolation of chloroform from the tissues is accomplished by distillation with steam, and the apparatus described under alcohol may serve here also, but the receiver should be surrounded with ice and provided with a mercury valve. As chloroform passes quickly into the circulation, an examination of the blood is of the greatest importance, and the acidity of the material under examination should be carefully noted. In case the reaction is neutral, a trace of tartaric acid should be added; if alkaline, a special examination must be made for formic acid, otherwise it will be impossible to say whether poisoning had been accomplished with chloroform or chloral, since the latter is decomposed by alkalis with the formation of chloroform.⁴



The slight solubility of chloroform in water also should not be neglected, so that even when no oil drops appear the aqueous distillate should, nevertheless, be submitted to the more sensitive tests for chloroform.

Tests.—1. On boiling a drop of chloroform with a mixture of 0.3 gram of resorcin in 3 c.c. of water and 3 drops of 10 per cent. sodium hydroxid, the fluid becomes yellowish red and shows a green-yellow fluorescence. The red color is probably due to sodium roseolate and the fluorescence to fluorescein. A slight modification of the reaction may be applied directly to the urine.⁵

2. Chloroform precipitates red cuprous oxid when boiled with

¹ McCardia, Brit. Med. Jour., 1898, i, 368.

² Dun, Glasgow Med. Jour., 1898, xlix, 347.

³ Weber, Internat. Clinics, 1920, 4, 54.

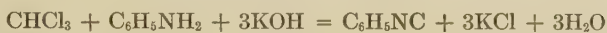
⁴ Liebig, Liebig's Annalen, i, 199.

⁵ Schwartz, Zeitschr. f. anal. Chem., xxvii, 668.

Fehling's solution. This reaction may be utilized for the quantitative determination of the poison. A measured amount of the reagent is heated in a pressure-bottle with the material in which chloroform is to be determined, and the precipitated cuprous oxid is reduced to copper in a stream of hydrogen and weighed; or the amount of unchanged copper may be determined with a standard solution of dextrose. Two equivalents of copper (2Cu) correspond to one equivalent of chloroform (CHCl_3):



3. On warming a mere trace of chloroform with a little anilin and alcoholic potassium hydroxid, the offensive and irritating odor of isobenzonitril is produced. The test will easily show the presence of 1 part of chloroform in 5000 parts of water:



This reaction is given also by chloral, bromoform, iodoform, and trichloroacetic acid.

4. When warmed with alpha- or beta-naphthol in strong caustic potash, chloroform produces a blue color, which, on exposure to the air, becomes green and finally brown.¹

5. On boiling with alcoholic potassium hydroxid, chloroform yields the triethyl ether of orthoformic acid:



After diluting with water and evaporating the alcohol, the material is acidified with tartaric acid and the formic acid distilled off and tested by reactions given on page 637 under Chloral.

6. A test for chloroform which renders others almost superfluous is founded on the decomposition of the substance by heat into perchlorobenzene, chlorin, and hydrochloric acid.² This reaction forms the basis of the Ragsky³ process, which should always be employed where circumstances point to chloroform, and especially when the amount of the poison (as in an examination of the blood) is known to be small. The material is introduced into a flask provided with a doubly perforated cork. Through one of the perforations passes a funnel tube, and through the other a delivery tube, bent at right angles. The flask is placed on a water-bath and connected with a piece of hard glass tubing 18 inches long, which is heated for about 4 inches by a broad Bunsen burner. About 4 inches in front of the heated portion the tube passes through a Liebig's condenser having a length of 6 inches, and beyond the condenser a piece of filter-paper, moistened with a mixture of starch-paste and potassium iodid, is placed in the tube.

¹ Lustgarten, Zeitschrift. f. anal. Chemie, xxii, 97; Monatsh. f. Chemie, iii, 722.

² Basset, Jahresb. d. Chemie, 1867, 608; Ramsay, Ibid., 1886, 628.

³ Jour. f. prak. Chem., xlv, 170.

The end of the tube is connected with a set of Liebig's bulbs containing a solution of silver nitrate, and these are in turn connected with an aspirator.

After the tube has been heated to bright redness the mixture in the flask is distilled at a gentle heat, while a current of air is slowly drawn through the system by the aspirator. Any chloroform vapor that may be present is decomposed for the most part according to the equation: $6\text{CHCl}_3 = \text{C}_6\text{Cl}_6 + 6\text{HCl} + 6\text{Cl}^1$ With 150 c.c. of blood taken from the carotid of a dog anesthetized with chloroform the writers were able to show all three products with the greatest ease. The perchlorbenzene forms beautiful needles just in front of the flame; the chlorin decomposes the potassium iodid, liberating iodine, which turns the starch blue, and hydrochloric acid, passing into the bulbs, precipitates silver chlorid which may be identified by appropriate tests.

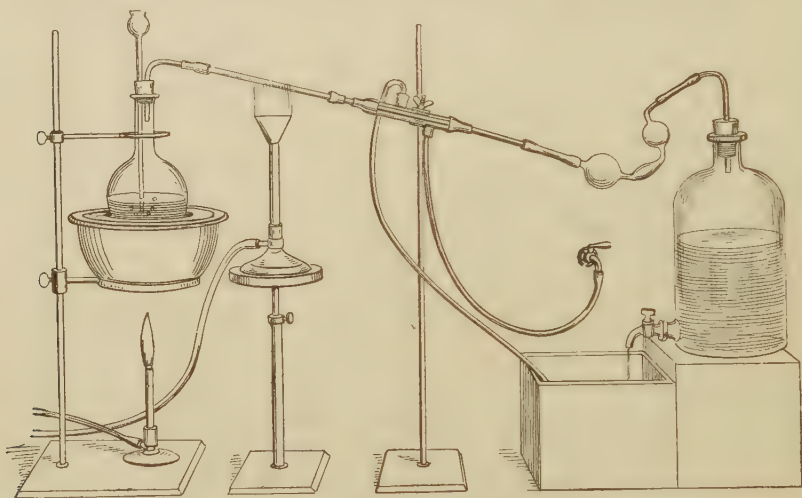


FIG. 62.—Apparatus for detecting chloroform by the Ragsky process.

If the presence of chloroform is thus indicated, the heating of the tube should be discontinued and the distillate collected in a pointed tube. Any oil drops which may thus be collected should be submitted to the tests given above.

In the Maxwell case the presence of chloroform was demonstrated by Luedeking² in the body of the victim twelve days after death from the inhalation of chloroform, and in the bodies of dogs killed in this manner after they had been permitted to decompose for four weeks. Maxwell afterward confessed that he had given chloroform. Luedeking used the lungs for analysis, and cites as a partial explanation of the tenacity with which chloroform is held by the tissues that a solution

¹ At a dull red heat monochlorethane and tetrachlorethylene are formed at the expense of perchlorbenzene (see Ramsay and Young, *Jahresbericht u. d. Vorts. d. Chemie*, 1886, 628).

² *Amer. Chem. Jour.*, 1886, 358.

of chloroform water will respond without difficulty to the tests for chloroform after it has been exposed to the air for two weeks.

Animals dying from other causes and left to decompose for ten days to four weeks gave no reaction by the Ragsky process simulating that produced by chloroform.

7. Cyan Reaction (*W. Heinz and A. W. Hofmann*).—Place some of the suspected distillate plus some ammonium chlorid plus alcoholic KOH solution into a fair-sized hard glass tubing. It is sealed by fusing and is put into a hot-water bath for several hours. The following reaction takes place: $\text{CHCl}_3 + 2\text{NH}_3 + 3\text{KOH} = \text{NH}_4\text{CN} + 3\text{KCl} + 3\text{H}_2\text{O}$. In the reaction product the cyanid is then tested for.

Quantitative Estimation (*E. Ludwig*).—Flask (*a*) contains a little pure water, enough to serve as a valve for the 2 glass tubes running to the bottom of the flask. Tube (*b*) contains glass beads. U-shaped tube (*c*) contains silver nitrate solution. To start the determination, the tube and beads within it are heated to a faint glow. The chlorin-free air is drawn through the apparatus from left to right.

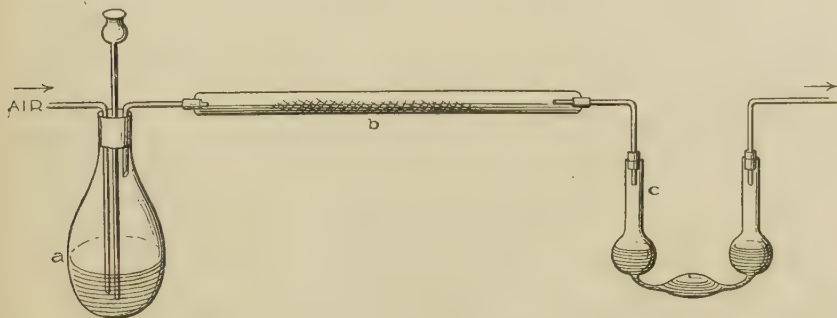


FIG. 63.—Ludwig's apparatus.

All the air going through the apparatus must pass through the silver nitrate solution. If after a few minutes no turbidity is noticed in the silver nitrate solution, the air passing through and the water in the flask are chlorin free. The next step is to add a measured amount of the distillate containing the chloroform, through the thistle tube, into flask (*a*). It is then put in a warm water-bath at 60°C . (140°F .). The stream of air passing through gradually forces all the chloroform through the red-hot tube. Here the CHCl_3 is burned, converting all the chlorin into HCl . This passes on and is collected in U tube in the form of AgCl . When all the chloroform has been burned up, the AgCl is collected, washed, and weighed. From this weight the amount of chloroform is calculated.

Second Method.—Nieloux method¹: To 20 c.c. of blood, or other aqueous liquid, 95 c.c. of alcohol and 5 c.c. of a 5 per cent. alcoholic solution of tartaric acid are added. The mixture is placed in a Kjeldahl

¹ C. 1. Soc. de biol., 1906, lx, 88. See Buckmaster and Gardner, Proc. Roy. Soc. London, 1907, 79, B., 309.

flask fitted with a cork through which passes one tube of a Reitmaier bulb upon whose other tube a continuation has been fused, which is bent downward and passes to the bottom of a graduated cylinder in such manner that its point is below the level of 10 c.c. of alcohol placed therein, and 40 c.c. are distilled over. All of the chloroform present passes into the distillate, which is then transferred to a flask, along with 10 c.c. of alcohol used to wash the cylinder. To the 60 c.c. now in the flask 10 c.c. of a 10 per cent. alcoholic solution of caustic potash (free from chlorid) are added, the flask is fitted with an Allihn, or other effective, reflux condenser, and the contents are boiled moderately for an hour. After cooling, the contents of the flask are transferred to a beaker and 15 c.c. of water, used in two portions to wash the flask, are added. The contents of the beaker are accurately neutralized with sulphuric acid, using phenolphthalein as indicator, 0.5 c.c. of a 5 per cent. solution of neutral potassium chromate are added, and the liquid titrated with a standard solution of silver nitrate containing 8.535 gm. to the liter, 1 c.c. of which represents 2 mgm. of chloroform. The process is affected with a minus error of 2 per cent., which is constant. Tissues are hashed and mixed with 95 c.c. of alcohol, and 5 c.c. of 5 per cent. alcoholic tartaric acid solution to 20 gm. of tissue and the process carried on as above.

This method presents two decided advantages over such methods as that of Ragsky, which it at least equals in accuracy. It consumes less time. It yields the whole of the chloroform present in alcoholic solution, and particularly, if proportionately larger quantities of substance and reagents be employed, an aliquot part of the distillate may be used for the quantitative determination, and the remainder for the identification tests.

BROMOFORM

Bromoform (Bromoformum, U. S. P.) is a heavy, oily liquid very similar to chloroform. The vapor produces general anesthesia, but the liquid is not sufficiently volatile to be used as a practical anesthetic; the vapor is irritating to the eyes and respiratory passages. Administered in the liquid form it has been used in the treatment of convulsive affections, especially whooping-cough; a number of cases of poisoning, for the most part not fatal, have been reported.¹ It is usually administered as an emulsion and the heavy bromoform has a tendency to settle to the bottom of the bottle; a number of cases of poisoning have resulted from the taking of the last dose in the bottle.² The symptoms are very similar to those caused by chloroform taken internally; there are intoxication, sometimes excitement,³ then a tendency to sleep, anesthesia, feeble respiration, contracted pupils, coma. Three drops are said to have caused serious symptoms in a child of four; a child of the same age was severely, but not fatally, poisoned by 15 or 20 minims (2.6 or 3.5

¹ Börger, Münch. med. Woch., 1896, 43, 469; Cheney, Arch. of Pediatrics, 1887, 14, 112.

² Burton-Fanning, Brit. Med. Jour., 1901, i, 1202; Watson, Ibid., 1920, ii, 702.

³ Weitz, Festsch. d. allg. Krankenh., St. Georg, Hamburg, 1912.

gm.).¹ About 1 dram (3.75 c.c.) caused the death of a child of two years in five hours²; convulsions occurred in this case.

Recovery has followed 4, 6, and perhaps 9 gm. The treatment consists in thoroughly washing out the stomach,³ and the administration of camphor or coffee⁴; artificial respiration has been necessary.

Long-continued administration of bromoform to animals causes fatty degeneration of various organs, similar to that produced by chloroform.

Properties.—A colorless, heavy liquid, boiling at 148° to 150° C. (298.4° to 302° F.), specific gravity of 2.9. It has a sweetish taste and odor similar to chloroform.

Isolation.—The same method is used as for chloroform.

Tests.—Bromoform yields the same reactions as chloroform, namely, isonitrile reaction, naphthol, resorcin, and Ragsky tests. To differentiate bromoform from chloroform, the precipitated silver halid in the Ragsky test is analyzed for the nature of the halid. The silver halid is filtrated and dried. It is then fused with a sodium and potassium carbonate mixture. This fusion, after cooling, is thoroughly leached and filtered. To the filtrate, which now contains the halid in the form of an alkali salt, is added sulphuric acid until acid in reaction. A small amount of fuming acid is now added, and then shaken out with chloroform. The brown color of the chloroform indicates the presence of bromin, and therefore bromoform.

Estimation.—For the quantitative determination of bromoform, the same method as used for chloroform is applicable.

METHYLENE, ETHYLENE, AND ETHYLIDENCHLORID

These substances are closely related in properties to chloroform. They, however, do not give the isonitrile, naphthol, and resorcin reactions. If boiled with alcoholic sodium hydroxid solution, they yield, among other products, monochlorethylene (vinylchlorid), which is recognized by its garlic odor. Chloroform does not yield this product.

METHYL BROMID

A number of cases of poisoning, some fatal, from the inhalation of *methyl bromid* (CH_3Br , a gas used in the manufacture of antipyrin and certain dyes), have recently been reported from Germany.⁵ There was unconsciousness, but also clonic and tonic convulsions, and other indications of irritation of the central nervous system; the compound disappeared from the body rapidly and none was found at autopsy.

¹ Dean, *Lancet*, 1893, i, 1062.

² Müller, *Münch. med. Woch.*, 1908, 55, 1211.

³ Compare Walldorf, *Med. Klin.* 1909, 5, 1784.

⁴ Rattner, *Deut. med. Woch.*, 1916, 42, 854.

⁵ Goldschmid and Kuhn, *Zentralbl. f. Gewerbehyg.*, 1920, 8, 28; Rohrer, *Vierteljahrsh. ger. Med.*, 1920, 60, 51; Loeffler and Rütimeyer, *Ibid.*, 60.

DIMETHYL SULPHATE

Cases of poisoning have resulted from exposure to the vapor and the liquid form of *dimethyl sulphate*, a very important methylating agent in the dye industry. Mohlau¹ reports 2 such cases. Shortly after exposure the only effects noted were slight irritation of the throat and eyes. As time progressed, the irritation of the throat and eyes intensified, and bronchial inflammation became progressively worse. Cyanosis became aggravated. These symptoms were followed by acute congestion of the lungs and edema of the throat and larynx. Recovery was slow, chronic irritation of the throat and eyes persisting. The action of the compound appears to be due to its hydrolysis to methylsulphuric acid and methyl alcohol. In the treatment of the conjunctivitis, Mueller² recommends the use of carron oil.

CARBON TETRACHLORID

Carbon tetrachlorid (tetrachlormethane, CCl_4), which has come into extensive use as a non-inflammable fat and rubber solvent, for use in some kinds of paint, as a delousing agent and as an anthelmintic, for use in fire extinguishers, etc., has a narcotic action similar to that of chloroform,³ but in addition causes convulsions, and is said to be more injurious to the heart.

Serious poisoning, and at least 1 death,⁴ has resulted from its use as a dry shampoo. In a case which recovered,⁵ there was unconsciousness, convulsive movements, nausea, and a long continued condition of hebetude; the carbon tetrachlorid, as is often the case, was contaminated with carbon disulphid.

Workers using carbon tetrachlorid as a solvent in rubber works complained⁶ of irritation of the eyes, nose, and throat; of dermatitis, and of loss of appetite and of weight. Anemia and toxic jaundice are reported.⁷

When used as a fire-extinguisher there may be some decomposition of carbon tetrachlorid into phosgene (COCl_2),⁸ chlorine, and hydrochloric acid, and under some circumstances poisoning with these substances result.

Properties and Tests.—This substance is also closely related to chloroform in properties. It is isolated by distillation.

Carbon tetrachlorid gives the isonitrile reaction. It does not give the naphthol and resorcin reaction. It does not give vinyl chlorid (garlic odor) by boiling with alcoholic KOH.

¹ Jour. Ind. Hyg., 1920, 2, 239; see also Weber, Chem. Centralbl., 1902, 1, 364.

² Chem. Met. Eng., 1920, 23, 833.

³ Colman and Marshall, Lancet, 1907, 1, 1709; Waller, Ibid., 1909, ii, 369, 1307; Lehmann, Arch. f. Hyg., 1911, 74, 1; Cf. Hall, Jour. Agr. Res., 1921, 21, 157.

⁴ Velej, Lancet, 1909, ii, 1162.

⁵ Levassort, Jour. Amer. Med. Assoc., 1913, 60, 1719.

⁶ Hamilton, Bull. 179, U. S. Bureau of Labor Statistics, 1915, 32.

⁷ A. D. H., Brit. Med. Jour., 1920, ii, 497.

⁸ Fieldner, Jour. Franklin Inst., 1920, 190, 543. See also under Chloroform, p. 640, Carbon Monoxid, p. 296, and Phosgene, p. 396.

TETRACHLORETHANE

Tetrachlorethane ($\text{CHCl}_2\text{—CHCl}_2$, sym. tetrachlorethane, acetylene tetrachlorid), prepared industrially by the action of chlorin upon acetylene, is a heavy, colorless, oily liquid with a boiling-point of 147°C . (296.6°F .) and a specific gravity of 1.614. The vapor is about six times as heavy as air, a very important fact in connection with the dangers from the industrial use of the substance. It is non-inflammable and has a sickish sweet odor suggestive of chloroform. It is an excellent solvent for certain types of cellulose esters, resins, etc., and was extensively used during the war as an ingredient of some of the airplane "dopes," or varnishes, with which the wings and other parts of airplanes were painted; it is used in the manufacture of non-inflammable films, lacquered goods, artificial silk, etc.

Lehmann and his co-workers¹ in 1911 showed in animal experiments that the vapors of tetrachlorethane have a narcotic action similar to that of chloroform, but that they are about four times as toxic as the latter; Willcox found that animals anesthetized with tetrachlorethane recovered very slowly, twenty-four hours, or more, being sometimes required.

Up to the present the only serious cases of poisoning reported in man have been chronic or subacute, and have resulted from the inhalation of the vapor in its industrial use.

The first cases were observed in Germany in 1913,² and shortly afterward in England.³ The cases occurred in airplane factories; the outstanding symptom was jaundice. It was found that the poisoning was associated with the use of "dope," one constituent of which was tetrachlorethane; the German preparation contained more than 60 per cent., the English about 12 per cent. of this compound, together with a number of other solvents. By means of animal experiments Heffter and Joachimoglu,⁴ and Willcox⁵ showed that tetrachlorethane was the substance responsible for the symptoms in man.

Grimm⁶ in 1914 gave details of 18 cases of poisoning in Germany; in England at least 70 cases of jaundice with 12 deaths occurred. Apparently no fatal cases, or even cases of very severe poisoning, have occurred in the United States,⁷ and with the knowledge at present available, and the increased care in its use, there seems to be no reason to fear that they will occur.

Occasionally men may be overcome by the vapors acutely, when exposed to an unusually high concentration as when the substance is spilled over the clothes; in such cases unconsciousness and respiratory failure (as in chloroform poisoning and requiring artificial respiration) has occurred.⁸

¹ Lehmann, Arch. f. Hygiene, 1911, 74, 1.

² Jungfer, Zentralbl. f. Gewerbehyg., 1914, 2, 222.

³ Willcox, Lancet, 1914, ii, 1489.

⁴ Heffter and Joachimoglu, Vierteljahrs. f. ger. Med., 1914, 48, II Suppl., 192.

⁵ Willcox, Loc. cit.

⁶ Grimm, Vierteljahrsch. f. ger. Med., 1914, 48, II Suppl., 161.

⁷ Hamilton, Jour. Amer. Med. Assoc., 1917, 69, 2037; Parmenter, Jour. Ind. Hyg., 1921, 2, 456.

⁸ Hamilton, Loc. cit.

Parmenter has described the early symptoms of poisoning among those exposed for a considerable period to the vapors of tetrachlorethane in detail: they begin with abnormal fatigue, discontent, general nervousness, and loss of appetite; then follow nausea, vomiting, and dizziness. The blood at this stage of poisoning is striking and is of aid in diagnosis¹: there is a progressive increase of large mononuclear cells, often reaching 40 per cent.; there are many immature large mononuclears, a slight elevation in the white count, and a progressive but slight anemia. Removal of the patient from exposure to the tetrachlorethane at this stage leads to prompt recovery.

The symptoms² in severe or fatal cases as they developed in the airplane factories were described about as follows: general malaise, drowsiness, vomiting, constipation, and headache, followed after a period of days or even weeks by intense jaundice with pale stools and bile-stained urine; vomiting became worse; confusion, stupor, delirium, coma, and death followed. A purpuric rash, hemorrhages, hematemesis; also convulsions and suppression of the urine occurred. If the patient was removed from the exposure when the jaundice was slight, complete recovery occurred, but slowly. In cases with deep jaundice recovery was unlikely. Occasionally the patient recovered from the acute symptoms but later developed ascites with signs of contraction of the liver. The jaundice is attributed to a cholangitis set up in the smaller bile-ducts causing an obstruction of the bile.

In some of the German cases where the exposure was to more concentrated vapors, nervous symptoms (tremors, anesthetics, knee-jerk variable, numbness, excessive sweating) were marked.³

Postmortem Appearances.—There was a marked fatty degeneration of the liver cells; in severe cases there was a necrosis of the liver cells and a condition of acute yellow atrophy. The affected area was in more prolonged cases, replaced by fibrous tissue. There was fatty degeneration in the kidneys.

The **treatment**⁴ consists in prompt removal from exposure and rest, and saline aperients; the administration of alkalis is recommended in cases of jaundice with toxic symptoms. The patient should not be permitted to return to his work for a long period (at least a month) after the jaundice has cleared up.

Cases of poisoning may be avoided by proper ventilation and careful medical control; under these conditions work with tetrachlorethane does not present greater hazards than that with benzene, lead, etc.⁵

iodoform

Most of the cases of poisoning with iodoform have been medicinal and have resulted from the too free use of the drug as a surgical dressing; a few cases have resulted from its internal administration.

¹ See Minot and Smith, *Arch. Int. Med.*, 1921, 28, 687.

² Willcox, *Lancet*, 1915, i, 544; Grimm, *Vrtljschr. f. ger. Med.*, 1914, 48, II Suppl., 161.

³ Grimm, *Loc. cit.*; Koelsch, *Münch. med. Woch.*, 1915, 62, 1567.

⁴ Compare Willcox, *Brit. Med. Jour.*, 1916, i, 300.

⁵ Parmenter, *Jour. Ind. Hyg.*, 1921, 2, 456; Frois, *Bull. Acad. Méd.*, 1922, 88, 40.

Properties.—Iodoform (Iodoformum, U. S. P., CHI_3) forms small lemon-colored, hexagonal crystals possessing a very penetrating, persistent, and disagreeable odor and taste; it is insoluble in water and soluble in alcohol, ether, glycerin, and fatty oils. It melts at 119°C . (246.2°F .), and is volatile with steam.

The **physiologic action** of iodoform is exceedingly complex. Part of the drug is absorbed as such and causes marked effects upon the brain, while part is decomposed by alkalis and proteins into iodine and iodids, and these exert their peculiar action upon various tissues. Moreover, the secretion of the thyroid gland is thought to be increased,¹ and the acceleration of the heart, which is so often observed in cases of poisoning with iodoform, is frequently attributed to this action. The local action of iodoform is not, as a rule, very marked, although at times it causes irritation in the neighborhood of the wound. The iodine of iodoform is chiefly excreted in the urine as iodids, but some is found in the saliva, sweat, and bronchial secretion. Some of the iodine is retained in the body for a very long time, and is excreted in the urine very slowly.

Symptoms.²—The symptoms of acute iodoform poisoning, as might be expected from what has been said above, are very complex and variable, and sometimes one symptom and sometimes another predominates. As seen after the free application of iodoform to a wounded surface, or to a bone cavity, they are frequently as follows: There may be general malaise for a few hours or a day, and then the more severe symptoms appear. The patient becomes sleepless and restless, may suffer from nausea, headache, giddiness, and mental confusion, and then pass into a condition of great depression resembling melancholia; hallucinations and delusions of persecution and suicidal impulses may follow. The period of depression may be followed by mania and violent delirium and other symptoms resembling meningitis. Coma, often continuing for several days, and finally collapse and death occur. At times the immediate effects disappear, but permanent insanity and dementia result. In other cases the delirium is of a mild type, and the delusions harmless but grotesque.³

The pulse in cases of iodoform poisoning is often very rapid. There is often high fever, but this may not be present. In some cases the symptoms of cerebral irritation are absent, the symptoms beginning with somnolence which deepens into stupor and collapse.

All the foregoing symptoms may occur after the removal of the dressings. The most frequent form of poisoning is that in which the effects are largely local. In these cases, which are frequently ascribed to an "idiosyncrasy," there are redness and painful swelling about the wound, and often a wide-spread eruption and lymphangitis and sometimes death—in one case after twenty days.

¹ Compare Hunt and Seidell, *Jour. Pharm. and exp. Ther.*, 1910, 2, 15.

² See Cutler, *Boston Med. and Surg. Jour.*, 1886, 115, 73, 101 (collection of 78 cases; mortality of 34 per cent.); Hirsch, *Zeits. f. Ohrenheilk*, 1911, 63, 340; Grossman, *Med. Rec.*, 1920, 98, 772; McLean, *Amer. Gyn. and Obstet. Jour.*, 1897, x, 249.

³ Black, *Brit. Med. Jour.*, 1885, i, 70.

The long-continued use of iodoform in wounds leads to a chronic form of poisoning in which the symptoms of cerebral excitement are but little marked. Dyspepsia and loss of weight, eczema, and other skin eruptions, palpitation of the heart, and sometimes amblyopia¹ are features of this form of poisoning.

Fatal Period.—The amount of iodoform necessary to cause death when taken internally is not known; individuals seem to differ greatly in their susceptibility to the drug. Thirty grains (1.94 gm.) and perhaps even 20 grains (1.29 gm.) have caused death, while recovery has followed the taking of 120 grains (7.77 gm.). Very severe symptoms have followed the application of 11 grains (0.71 gm.) of iodoform to the uterus,² but such a result must be regarded as extremely unusual. The poisonous effects caused by the absorption of iodoform from wounds depend, not upon the amount of iodoform in the wound, but upon the amount actually absorbed, and the conditions determining the absorption are not known. Death may occur in a day,³ or it may be delayed for weeks.

Treatment.—The dressings should be promptly removed upon the appearance of symptoms of poisoning, but even then they may continue or become more severe. Potassium bromid has been highly recommended. In grave cases intravenous or subcutaneous infusions of normal saline solutions are said to have given good results. In the severe cerebral cases the prognosis is bad.

Postmortem Appearances.—Fatty degeneration of the heart, liver, and kidneys is the most characteristic lesion. Edema of the pia mater and of the lungs and acute nephritis have been found in some cases.

Detection.—The material under examination is made alkaline with caustic potash, or acid with phosphoric acid, and submitted to distillation in steam. The distillate is treated with a few drops of caustic potash, and any iodoform present is shaken out with ether in a separating funnel. After the ether evaporates, which should occur at the room-temperature, the iodoform remains as hexagonal stars or other hexagonal forms which may be recognized under the microscope (see Fig. 60).

The odor of iodoform is very characteristic, but unfortunately this odor is often masked by other odors which are present in a distillate from an organic fluid. Lustgarten,⁴ therefore, suggests the following reaction, which will show the presence of a small fraction of a milligram of the substance:

1. To a portion of a solution of 20 parts of phenol or resorcin and 40 parts of sodium hydroxid in 70 parts of water are added a few drops of a solution of the suspected substance in alcohol, and the mixture is carefully warmed over a small flame. In the presence of iodoform a

¹ de Schweinitz, *Therap. Gaz.*, 1897, 21, 671.

² Bolowski, *Ibid.*, 1888, 12, 188.

³ Dunergey, *Gaz. hebdom. d. Sci. méd. de Bordeaux*, 1911, 32, 260.

⁴ *Monatssch. f. Chem.*, iii, 717.

red precipitate forms, which is soluble in alcohol with a carmin-red color. The red color is discharged by mineral acids and restored by alkalis. This red substance has all the properties of rosolic acid, and is produced by chloroform as well as by iodoform.

2. Iodoform also yields the odor of isobenzonitrile when warmed with anilin and alcoholic potassium hydroxid.

3. When the material is obtained in sufficient quantity, a portion may be fused with caustic potash and tested for iodine.

SULPHONMETHANE (Sulphonal)

Sulphonmethane was introduced into medical practice in 1888, and within six years had caused at least 18 deaths,¹ most of which were medicinal or accidental. In 1900, Taylor and Sailer² collated 34 fatal cases.

Properties.—Sulphonmethane (Sulphonal, sulphonmethanum, U. S. P.) is diethyl-sulphone-dimethyl-methane, $(\text{CH}_3)_2\text{C}(\text{SO}_2\text{C}_2\text{H}_5)_2$. It occurs in colorless, prismatic crystals that are without odor and nearly tasteless. They melt at 125°C . (257°F .). Sulphonmethane is sparingly soluble in cold, readily soluble in hot, water, and soluble also in alcohol and ether.

The **physiologic action** of medicinal doses of sulphonmethane is similar to that of paraldehyd—*i. e.*, it causes sleep, with but little depression of the circulation and respiration; its action is slower and not so certain. Sulphonmethane is eliminated by the kidneys partly as such, partly as ethylsulphonic acid; the elimination takes place very slowly, so that there is a tendency to a cumulative action.

Symptoms.—Medicinal doses, 7 to 15 grains (0.5–1 gm.), of sulphonmethane usually simply cause sleep, but sometimes nausea, headache, dizziness, and irregular gait result. After larger doses the symptoms are exceedingly variable; among those noted are the following: mental confusion; motor disturbances, as shown by an irregular gait or paralysis, stupor, and insensibility; more rarely excitement, and convulsions. In very severe cases the respiration is stertorous and irregular, the pulse scarcely perceptible, and there is marked cyanosis. There is sometimes some elevation of temperature. Death usually results from failure of the respiration, but it may occur although artificial respiration is maintained. Sometimes the secretion of urine is suppressed and death results from anuria. A very common feature, especially in the cases which continue for some time, is the appearance of hematoporphyrin in the urine; this pigment, which indicates an extensive destruction of the blood, causes the urine to assume a red color, and is an unfavorable symptom. Nearly all the cases of hematoporphyrinuria reported have occurred in anemic women. Skin eruptions may also follow a single large dose. Coma has continued for six days and recovery taken place.

The long-continued use of sulphonmethane leads to a form of

¹ Friedländer, *Therap. Monatsh.*, 1894, 8, 231.

² Taylor and Sailer, *Contributions from Pepper Laboratory*, 1900, 120.

chronic poisoning¹ in which headache, vomiting, obstinate constipation, albuminuria, and hematorporphyrinuria, various mental and motor disturbances, and various forms of skin eruptions have been described.

Fatal Dose.—The fatal dose is extremely variable; much depends upon the individual. Thirty grains (1.94 gm.) caused death in a neurasthenic woman in forty hours.² Death has frequently followed doses varying from 75 grains to 1 ounce (4.85–31 gm.). On the other hand, a boy of fifteen took over 3 ounces (93 gm.), and after sleeping ninety hours recovered.³ In many cases death has resulted after the long-continued use of comparatively small doses. Thus several deaths have followed the daily use of from 10 to 20 grains (0.64 to 1.29 gm.) for from two to twelve months.⁴

Fatal Period.—Death may occur in a few hours or days,⁵ or after months; it has occurred some time after the use of the drug was stopped.

Treatment.—The stomach should be washed out, and diuretics, purgatives, strychnin, and other stimulants administered. Much may be done to avert the poisonous symptoms, so often observed when the drug is used for some time, by observing certain simple precautions. The drug should be administered in solution in hot water, in order to secure more rapid and complete absorption; the administration should be interrupted every few days, and a full medicinal dose should not be repeated within twenty-four hours. Women should receive smaller doses than men. These precautions greatly diminish the tendency to the appearance of a cumulative action.

Case of Sulphonal Poisoning.—A woman, aged twenty-eight, suffering from melancholia and hysteric manifestations, but apparently free from organic disease, took 15 grains (0.97 gm.) of sulphonal; as wakefulness continued another dose of 15 grains (0.97 gm.) was given one hour and a quarter later. She slept for twelve hours; she could then be roused and would talk rationally, but when left alone, would fall asleep again. The temperature rose to 102° F. Respiration began to fail, and the patient became very cyanotic after about twenty-three hours; artificial respiration was maintained for several hours, the pulse continuing fairly good for some time. Death occurred forty hours after taking the drug.⁶

Isolation.—The finely divided material is evaporated to dryness on the water-bath (if blood, acidify first slightly with HCl), then extract with chloroform or benzol on the water-bath. Filter off the solvent, and then evaporate it. The residue is now treated repeatedly with small portions of petroleum ether in order to remove fats and pigments. The sulphonal is not soluble in petroleum ether, and will remain behind as a white residue. To purify it further from cholesterins, etc., the residue is taken up in water, and filtered. The aqueous filtrate is again extracted with chloroform (Kippenberger⁷).

¹ Pollitz, Wien. klin. Wochenschr., 1898, ii, 566; Waldo, Brit. Med. Jour., 1901, i, 1473; Rogers, Jour. Amer. Med. Assoc., 1912, 58, 1510.

² Case 1.

³ Neisser, Deutsch. med. Wochenschr., 1891, xvii, 702.

⁴ Pollitz, Loc. cit.

⁵ Knaggs, Brit. Med. Jour., 1890, ii, 955.

⁶ Pettit, Medical News, 1889, iv, 165.

⁷ Zeitschr. f. Untersuchung der Nahr. u. Genussorn, 1899, 2, 75.

D. Vitalli¹ suggests extracting the finely ground material three times with double its volume of hot 90 per cent. alcohol. Let cool and then filter. Distill off the alcohol from the combined filtered extracts. Make the residue slightly alkaline with KOH (to fix pigments and other impurities), and extract with ether. On evaporation of the ether it leaves the sulphonal as a residue, which can be further purified according to Kippenberger.

Tests.—1. When melted with potassium cyanid sulphonal develops an offensive mercaptan odor, and potassium sulphocyanate is formed at the same time. A blood-red color is therefore produced on the addition of ferric chlorid to a solution of the residue in water.² A careless execution of this test is somewhat dangerous to the experimenter.

2. When heated in a test-tube with powdered charcoal, sulphonal forms mercaptan, acetic acid, formic acid, and sulphur dioxid. The odor of mercaptan may be noted, and the vapors will change blue litmus-paper. Sulphur dioxid may be shown by its bleaching action on a piece of filter-paper moistened with blue starch iodid and suspended in the mouth of the tube.³

3. Heated with twenty times its amount of dry sodium acetate, fumes of H₂S develop; these blacken lead acetate paper, or color violet an alkaline sodium nitroprusside paper.

4. Heating with powdered iron yields a garlic odor, and the residue treated with HCl yields H₂S.

5. If 0.1 gram of sulphonal be heated in a test-tube with 0.1 gram of sodium salicylate, an odor of mercaptan develops; if this mixture be treated with 5 drops of alcohol and 5 drops of concentrated sulphuric acid, and after five minutes standing, heated with the addition of a further 5 drops of sulphuric acid, a turbid red solution is obtained, having the odor of methyl salicylate.

6. If 0.2 gram of sulphonal be ignited in a porcelain dish with 0.2 gram of sodium salicylate, a violet-colored residue is obtained, which gives a violet solution with a drop of water. If now, a drop of dilute hydrochloric acid be added, the color changes to yellow, a brown flocculent precipitate separates, and sulphur dioxid escapes. Trional gives these two latter reactions.⁴

Estimation.—The material is quantitatively extracted and purified according to Kippenberger's method (see above); the pure residue is dried and weighed.

TRIONAL AND TETRONAL

Trional (Sulphonethylmethanum, U. S. P.) is sulphonmethane in which one of the methyl groups has been replaced by an ethyl (C₂H₅) group; in tetronal both of the methyl groups have been replaced by ethyl. These compounds are very similar in both their chemical and

¹ Bull. chim. farm., 1900, 39, 461.

² Vulpus, Zeitschr. f. anal. Chemie., xxvii, 665.

³ Schwarz, Zeitschr. f. anal. Chemie., xxvii, 665.

⁴ See Zimmermann, Apoth. Ztg., 1920, 35, 27; Chem. Abs., 1921, 15, 1779.

physiologic properties to sulphonmethan,¹ but both have a bitter taste, and trional melts at 76° C. (169° F.), and tetronal at 89° C. (192° F.). Both compounds have caused fatal poisoning; the symptoms are very similar to those caused by sulphonal.²

Isolation.—Follow the same method as given for sulphonmethane.

Tests.—Both trional and tetronal give the same tests as sulphonal. To distinguish these hypnotics, a melting-point determination should be run on the recrystallized substance.

BARBITAL

Chemically barbital, which was introduced into medicine under the name "veronal," is diethylbarbituric acid (*Acidum diethylbarbituricum*, diethyl malonyl urea, malo-urea); $\text{CO}(\text{NHCO})_2\text{C}(\text{C}_2\text{H}_5)_2$; it is a ureid derived from diethylmalonic acid and urea. It³ is a white, crystalline powder, melting at 188° to 189° C. (370.4° to 372.2° F.), odorless and faintly bitter. It is soluble in about 150 parts of cold, and in about 12 parts of boiling, water; freely soluble in alcohol and ether. It forms salts with alkalis which are soluble in water; the sodium salt is used in medicine under the name barbital sodium ("veronal sodium," "medinal").

Barbital was introduced as a hypnotic in 1903. In 1905 Kress⁴ published a long list of cases in which untoward results had followed its use. Since then the number of cases of poisoning reported have rapidly increased; in England and Wales, 1911–13, it occupied seventh place as the cause of death from all poisons.

In England the use by the public of barbital is said to have largely superseded that of sulphonmethane when the latter was placed on the Poisons Schedule; the increasing number of deaths from "veronal" led to its being scheduled as a "poison," so that it can now be obtained only from registered pharmacists, who must label it "poison," keep proper records of the sales, etc.

Most of the cases of poisoning so far reported have been accidental. Some have been suicidal; it was taken for this purpose in 45 cases in Hamburg between 1904 and 1913.⁵

Cases of chronic poisoning and of habit formation ("veronalismus") began early to be reported.⁶

Barbital is a rather quickly acting hypnotic, producing sleep in about one-half hour. Respiration and circulation are little affected by medicinal doses. It is, perhaps, twice as active as hydrated chloral, but the zone between the effective and the toxic dose seems to be greater in the case of barbital than in that of chloral; in this sense barbital is a safer hypnotic than chloral. But this applies only to single doses. The

¹ Baumann and Kast, *Zeitschr. f. Physiol. Chem.*, 1890, xiv, 63, 64.

² Church, *Amer. Med.*, 1901, ii, 729; see also Young, *Univ. Med. Mag.*, 1896–97, ix, 715; Hart, *Amer. Jour. Med. Sci.*, 1901, 121, 435 (chronic).

³ New and Non-official Remedies, 1922, 57.

⁴ Kress, *Ther. Monatsh.*, 1905, 19, 467; cf. Seifert, *Die Nebenwirkungen d. moder. Arzneimittel*, 1915, 99.

⁵ Sieveking, *Vierteljahresch. f. ger. med.*, 1918, 56, 163; see also Boenheim, *Med. Klin.*, 1921, 17, 1263.

⁶ Kress, *Loc. cit.*; Laudenheimer, *Ther. d. Gegenw.*, 1904, 6, 47.

effect of barbitol is long continued, due to its slow elimination from the body; the conditions are thus favorable for a cumulative action, and many of the cases of poisoning reported have resulted from the taking, at too short intervals, two or more doses.

In animals toxic doses of barbitol¹ cause, in addition to the effects upon the central nervous system, a profound fall of blood-pressure due to a peripheral paralysis of the blood-vessels comparable to that caused by arsenic; there is also a fall of temperature.

Barbitol is excreted, unchanged, to the extent of 70 per cent. or more in the urine; the excretion is slow, sometimes not reaching the maximum until the second day and continuing on the third and even the fourth day after a medicinal dose.²

The **symptoms** in man have usually presented the picture of depression of parts of the central nervous system and stimulation of others. In some cases³ only deep unconsciousness, with absence of corneal reflex; shallow, feeble respiration, often ceasing for minutes at a time, sometimes Cheyne-Stokes; cyanosis; subnormal, sometimes elevated temperature; pulse usually good, but sometimes slow; death from respiratory failure. The pupils are often constricted and in some cases opium-poisoning has been suspected⁴; or the pupils may undergo alternate constriction and dilatation.⁵ Paralysis of some of the eye muscles, resulting in diplopia, has been reported; epidemic encephalitis has been suspected.⁶

In other cases⁷ there have been, in addition to stupor, excitement or restless sleep, trismus, exaggerated reflexes, dilated pupils, delirium, rise of temperature; the symptoms have suggested uremic coma, in other cases pneumonia.⁸ In cases of recovery, headache, dizziness, somnolence, double vision, ataxia, continuing for several days, are reported.

Various forms of skin rashes have often been reported⁹; these have occurred after 0.5¹⁰ and 1 gram.¹¹

Marked symptoms have followed two or three small doses taken within a few hours of each other. In one case¹² two doses of 0.75 gram were taken within eight hours; there was sound sleep for eleven hours

¹ Jacoby, Arch. exp. Path. u. Pharm., 1911, 66, 241.

² Fischer and Hoppe, Münch. med. Woch., 1909, 56, 1429.

³ Zörnleib, Wien. med. Woch., 1906, 56, 2454; Weitz, Festsch. d. allg. Krankenh. St. Georg, Hamburg, 1912; Moszeik, Med. Klin., 1920, 16, 233.

⁴ Ehrlich, Münch. med. Woch., 1906, 53, 559.

⁵ Raemer, Deut. med. Woch., 1919, 45, 1305; 12 cases.

⁶ Hassin and Wien, Jour. Amer. Med. Assoc., 1920, 75, 671; MacLeod, Med. Rec., 1920, 98, 985.

⁷ Schneider, Prager med. Woch., 1907, 32, 17; Hald, Centr. f. Nervenhe. u. Psych., 1904, 27, 369; Gerhartz, Berl. klin. Woch., 1903, 40, 928; Nienhaus, Kor. Bl. f. Schw. Aerzte, 1907, 37, 336; see Hage (Vrtljschr. f. ger. Med., 1921, 3 S., 62, 19 and 223) for a good bibliography.

⁸ Willcox, Lancet, 1913, ii, 734, 1178.

⁹ House, Jour. Amer. Med. Assoc., 1907, 48, 1348; Woolley, Ibid., 1907, 49, 2153; Wolters, Med. Klin., 1908, 4, 182.

¹⁰ de la Harpe, Therap. Monatsh., 1909, 22, 108.

¹¹ Davids, Berl. klin. Woch., 1904, 41, 829.

¹² Topp, Therap. Monatsh., 1907, 21, 163.

and great dizziness and tendency to fall for three days; 0.5 gram on two successive nights caused dizziness, faintness, disturbed sensorium, and an erythema.¹ A man took 70 grains (4.7 gm.) in the course of thirty-six hours and slept for seven days²; there was low muttering delirium, absence of reflexes, rigid jaw, profuse salivation.

Small doses taken daily for some time have caused a condition resembling alcoholic intoxication with disturbances of speech, also hallucinations, delusions, tremors, ataxia,³ loss of memory, loss of weight, anemia, hematorporphyrinuria, and oliguria⁴; in mild cases there are dulness, drowsiness, nausea, vertigo, asthenia, skin rashes.⁵ Diagnosis is aided by examination of the urine.

Fatal Dose.—Death is stated to have followed the taking of 15 grains (1 gm.)⁶; it has resulted from 6 or 7 grams⁷; from 8 grams⁷; from 10 grams⁸; from 11 grams,⁹ and frequently from doses of 12 to 15 grams. Recovery has followed 9 grams,¹⁰ and 8 grams,¹⁰ and 6 grams,¹¹ but very severe poisoning has followed doses of 3 to 5 grams.¹²

In a case reported by Willcox a man of sixty-two recovered after 53 grains (3.5 gm.) of "veronal," but he was comatose for twenty-four hours. In another case a man took 125 grains (8.3 gm.), and remained unconscious for seventy to eighty hours, but recovered.¹³ Littell¹⁴ reports recovery after the taking of 120 grains (8 gm.) on each of twelve successive days, on gross symptoms of injurious effects being manifest until the end of that period.

Recovery followed 110 grains (7.3 gm.).¹⁵

From these and other cases 8 to 9 grams have been given as a dose which would ordinarily be fatal, but Willcox thinks that 50 grains (3.3 gm.) may be taken as an average minimum fatal dose.

Fatal Period.—Even with large doses death seems seldom to occur under twenty hours; in Ehrlich's cases (11 and 15 gm.) death occurred in twenty hours; in a case reported by Zörnlaib (8 to 10 gm.) it occurred in twenty-four hours, in another (6 gm.) in three days; in a case reported by Schneider (11 gm.) it occurred in forty-six hours; after 20 grams¹⁶

¹ Klausner, Fortsch. d. Med., 1910, 28, 107.

² MacLeod, Med. Rec., 1920, 98, 985.

³ Hoppe, Deut. med. Woch., 1905, 31, 971; Hoeftmann, Ibid., 971; Willcox, Lancet, 1913, II, 734, 1138.

⁴ Dobrschansky, Wien. Med. Presse, 1906, 47, 2150; Laudenheimer, Ther. d. Gegenw., 1904, 6, 47; Steinitz, Ibid., 1908, 10, 204.

⁵ Vallon and Bessière, L'Encephale, March, 1913, 33, 245.

⁶ Willcox, Lancet, 1913, ii, 734, 1178.

⁷ Zörnlaib, Wien. med. Woch., 1906, 56, 2454; Davies, Brit. Med. Jour., 1909, ii, 1154; Frazer, Lancet, 1914, i, 1736.

⁸ Weitz, Festsch. d. allg. Krankenk. St. Georg, Hamburg, 1912.

⁹ Ehrlich, Münch. med. Woch., 1906, 53, 559; Schneider, Prager med. Woch., 1907, 32, 17.

¹⁰ Hald, Centr. f. Nerven- u. Psych., 1904, 27, 369.

¹¹ Alexander, Brit. Med. Jour., 1913, ii, 20.

¹² Gerhartz, Berl. klin. Woch., 1903, 40, 928; Nienhaus, Kor. Bl. f. Schweiz. Aerzte, 1907, 37, 336; Geiringer, Wien. klin. Woch., 1905, 18, 1243.

¹³ Chitty, Lancet, 1913, i, 917.

¹⁴ Jour. Amer. Med. Assoc., 1921, 77, 1333.

¹⁵ Eckel, New York Med. Jour., 1909, 90, 118.

¹⁶ Embden, Münch. med. Woch., 1908, 55, 1050.

it occurred in thirty-six hours; after 200 to 250 grains it did not occur for seventy-nine hours¹; it has been delayed for one hundred hours. Recovery has followed after six days of coma.

Postmortem.² pulmonary edema, hyperemia and edema of the meninges, and hyperemia of the liver and kidneys have been described; the kidneys have shown extensive degeneration of the epithelium of the tubules; the heart usually shows marked dilatation, but the post-mortem signs are not characteristic.

Treatment.—The stomach should be washed out, especially if the poison has been recently taken; diuretics and purgatives are also recommended. Efforts should be made to maintain the blood-pressure by compression of the extremities, the administration of camphor³ and other cardiac and vascular stimulants, the injection of normal saline solution, etc.

Isolation.—The finely ground tissue slightly acidified with HCl is extracted with alcohol. The filtered alcoholic extract is evaporated to a thick syrup. The residue is taken up with hot water and filtered. The cooled filtrate is extracted with ether. On evaporating the ether, the veronal remains in the residue as needle-like crystals. By repeating the above process the material can be purified. In cases of veronal poisoning the urine is of first importance for analysis. Barbitol is excreted unchanged in the urine and in fatal cases (in which the patients usually live for twenty-four hours or longer) a very considerable amount may be found in the urine.⁴ The above method of isolation is applicable or the urine may be treated with lead acetate, filtered, and the excess of lead may be removed with H₂S and the filtrate concentrated prior to the extraction.⁵

Tests.—1. With mercurous nitrate it gives a white precipitate.

2. With Millon's reagent it gives a gelatinous yellow precipitate, soluble in excess.⁶

3. Equal parts of the crystalline residue and caustic alkali are fused for about two minutes. The cooled mass is dissolved in a little water, and divided into equal parts. In one portion the formed prussic acid is identified. The second portion is acidified with sulphuric acid and extracted with ether. On evaporating the ether diethyl acetate remains as an oily residue with a rancid odor. This with dilute ferric chlorid gives a red color.⁷

4. If some of the dry residue is sublimed, the following tests can be applied:

(a) A solution of chloro-iodid of zinc added to the sublimate gives a precipitate of small flat tabular crystals, gray to blackish-red in color.

¹ Germann, Jour. Amer. Med. Assoc., 1906, 46, 1999.

² Schneider, Prager med. Woch., 1907, 32, 17; Wilcox, Lancet, 1913, II, 734, 1178; Husemann, Vierteljahrsh. ger. Med., 1915, 50, 43.

³ Leo, Deut. med. Woch., 1913, 39, 591; Husemann, Loc. cit.

⁴ See Fischer and Hoppe, Münch. med. Wehnschr., 1909, 56, 1429.

⁵ See Frerichs, Arch. der Pharm., 1906, 244, 86.

⁶ See Molle and Kleist, Arch. der Pharm., 1904, 242, 401.

⁷ Jorissen, Jour. Pharm. et Chimie, 1911, 3, 478.

- (b) Hydriodic acid dissolves veronal sublimates, and often deposits large flat red crystals.
- (c) Potassium bromid solution of bromin gives flesh-colored needles and leaflets.
- (d) If dissolved in ammoniacal copper solution and allowed to evaporate; gives violet and pink monoclinic plates.

Estimation.—The purified crystalline veronal obtained from a thorough extraction of the tissue or of the urine is weighed as such. Van Itallie and Steenhauer¹ recommends the use of ethyl acetate for extracting the barbital from the urine, feces, and tissues. After extraction the substance is best purified by treatment with potassium permanganate in acid solution. By this method they were able to recover 100 per cent. of added veronal from the urine, and 97 per cent. from the organs.

Phenobarbital (phenyl-ethyl-barbituric acid; phenyl-ethyl-malonyl-urea), introduced as "Luminal," differs from barbital in that one ethyl (C_2H_5) group has been replaced by a phenyl (C_6H_5) group. Phenobarbital is almost insoluble in cold water, but, like barbital, forms a soluble sodium salt which is also used in medicine. Phenobarbital is a more active hypnotic than barbital, with little tendency to cause excitement. Severe symptoms—dizziness, nausea, vomiting, double vision—resulted from a dose of 0.3 gram.² Disturbances of speech, ataxia with inability to stand, and diminished reflexes followed the taking of 0.6 gram in twenty-four hours, and in another case, 0.9 gram (with 0.2 gram barbital) in four hours.³ Doses of 0.1 gram three times daily continued for eleven days, and in another case, for four weeks, caused diarrhea and an eruption resembling that of scarlet fever, covering the whole body except the face and hands.⁴ Coma, loss of reflexes, anesthesia of the skin, severe disturbances of pulse and respiration, amaurosis continuing for twenty-two days followed a dose of 2.4 grams taken with suicidal attempt.⁵ Death followed the taking of 15 grams of luminal sodium in the course of three weeks.⁶

Skin rashes have been reported many times.⁷

Poisoning has been reported⁸ from "dial," a compound containing two allyl groups instead of two ethyl groups, as in barbital; differentiation from diabetic and uremic coma was said to be difficult. Animal experiments showed "dial" to be more than twice as toxic as barbital.⁹

¹ Pharm. Weekblad., 1921, 58, 864, 1062; Chem. Abs., 1921, 15, 2893, 3363.

² Stein, Therap. Halbsmonatshft., 1920, 34, 387.

³ Farnell, Jour. Amer. Med. Assoc., 1913, 61, 192.

⁴ Haug, Münch. med. Woch., 1919, 66, 1494.

⁵ Ungár, Wien. klin. Woch., 1914, 27, 847.

⁶ Hueber, Münch. med. Woch., 1919, 66, 1090.

⁷ Haug, Loc. cit.; Pernet, Brit. Med. Jour., 1913, ii, 312; Curschmann, Therap. Monatshft., 1917, 31, 148; Strauss, Ibid., 338; Luce and Feigl, Ibid., 1918, 32, 236; Meissner, Ibid., 1919, 33, 332; Weber, Ibid., 1921, 35, 467; Phillips, Jour. Amer. Med. Assoc., 1922, 78, 1199; Wetselaar, Pharm. Weekblad., 1922, 59, 521.

⁸ Müller, Schw. med. Woch., 1920, 50, 973; Christoffel, ibid., 1123.

⁹ Report of Council of Pharmacy and Chemistry, Jour. Amer. Med. Assoc., 1920, 74, 266.

ORGANIC ACIDS OF THE FATTY ACID SERIES

ACETIC ACID (CH_3COOH)

From the standpoint of toxicology *acetic acid* is the most important of this group. Prior to near the close of the last century poisoning by acetic acid was very rare; at that time "essence of vinegar" (about 80 per cent. acetic acid) came into extensive use in parts of Europe and the number of cases of poisoning rapidly increased. In 1909 Franz¹ collected 256 cases of acetic acid poisoning in Germany; 46.2 per cent. of these occurred in children, with a mortality of 71.1 per cent. In St. Petersburg in 1908, 34 per cent. of all suicides were committed with acetic acid and 72 per cent. of all cases of poisoning were due to this acid. Similar figures are given for other Russian cities.² In the United States and England poisoning by acetic acid seems to be rare (4 fatal cases in England and Wales in 1912).

The symptoms are very similar to those caused by the mineral acids (q. v.), but in nearly all cases there is irritation of the respiratory passages. Death usually occurs within forty-eight hours. There is little accurate information as to the fatal dose; in many cases death is said to have followed "a swallow"; 2 tablespoonfuls were fatal³ to an adult, and a few drops have been fatal to children. Stumpf⁴ reported a fatal case of poisoning by a tablespoonful of the "essence of vinegar"; the man, aged thirty-two, suffered from severe diarrhea and a weak heart. Death occurred on the third day; for two days before death the patient had been in a condition of stupor. In a case reported by Birkett⁵ 2 or 3 ounces (59.2 or 89 c.c.) of 33 per cent. acetic acid were swallowed by an intoxicated man; in addition to the severe gastric symptoms there was laryngeal obstruction necessitating tracheotomy. Recovery followed.

Properties.—Pure acetic acid, glacial acetic acid, forms a colorless crystalline mass which melts at 17° C. (62.6° F.) to a colorless corrosive liquid having a specific gravity of 1.05, producing blisters on the skin, and boiling at 118° C. (244.4° F.).

Isolation and Detection.—The material is acidified with sulphuric acid and distilled with steam. The distillate, which is acid if acetic acid is present, is exactly neutralized with sodium hydroxid, and evaporated to dryness. A little of this residue warmed with sulphuric acid develops the odor of acetic acid. If alcohol is now added to this mixture, the odor of ethyl acetate is produced. Another portion of the dry residue, heated with arsenious acid in a dry hard glass tube, develops the disagreeable odor of cacodyl.

¹ Franz, *Friedreich's Blätter f. ger. Med.*, 1909, ix, 401; 1910, lxii, 35; cf. Bleibtreu, *Münch. med. Woch.*, 1908, 55, 1987.

² Schibkow, *Vierteljahrsh. f. ger. Med.*, 1918, 55, 187.

³ Bleibtreu, *loc. cit.*

⁴ Stumpf, *Münch. med. Woch.*, 1898, 45, 690.

⁵ Birkett, *Lancet*, 1867, ii, 98.

FORMIC ACID (HCOOH)

Formic acid resembles acetic acid, but is more volatile and more irritant; workmen using it suffer from dermatitis. Formic acid (0.1 to 0.25 per cent.) has been used as a food preservative. When given *per os* formic acid is oxidized by the body with difficulty, but it does not seem to act distinctly differently from acetic acid when fed to animals over long periods.¹

Properties.—A colorless, irritating liquid, causing blisters when applied to the skin. It solidifies at 1° C. (33.8° F.) and melts at 9° C. (48.2° F.), while it boils at 99° C. (210.2° F.). It mixes with water and alcohol. Formic acid has a reducing action, as it is readily oxidized to carbon dioxid, and therefore precipitates silver solutions.

Isolation and Detection.—The urine is of first importance in the detection of formic acid, which is rapidly excreted as a formate. The material, acidified with sulphuric acid, is distilled with steam in the usual manner. If formic acid be present, the distillate will have a strong acid reaction. It is exactly neutralized with sodium hydroxid, and evaporated to a more concentrated form.

If a little of this solution be warmed with some mercuric chlorid it precipitates mercurous chlorid. If warmed with silver nitrate solution it precipitates black metallic silver.

TARTARIC ACID (HOOC—CHOH—CHOH—COOH)

Tartaric acid is sometimes used as an ingredient of lemonade; very serious poisoning has resulted from neglect to dilute the mixture. When injected hypodermically into animals or given *per os* in very large doses (3 gm. per kilo. body weight) the tartrates cause nephritis in animals,² but there is no ground for fearing that this occurs in man from therapeutic doses.³

Properties.—Tartaric acid is tetravalent and bibasic, and forms large monoclinic prisms which melt at 170° C. (338° F.), and are readily soluble in water and alcohol, but difficultly soluble in ether. Its solutions are dextrorotatory. Its salts are called tartrates.

Isolation.—It is extracted with water. This aqueous extract is evaporated to a syrupy consistency. To this, five times the volume of alcohol is added. After standing some time it is filtered and the alcohol evaporated. This process is repeated. On the final evaporation tartaric acid remains in crystalline form in the residue in a more or less impure form.

Tests.—1. Add a few drops of 1 per cent. resorcin solution and about 3 c.c. of strong sulphuric acid and heat slowly. Tartaric acid is indicated by a rose-red color which is discharged on dilution with water.

2. Extract 5 grams of the sample with absolute alcohol and evapo-

¹ Sollman, Jour. Pharm. and Exp. Therap., 1921, 16, 463; cf. Heffter and Rubner, Vrtljschr. f. ger. Med., 1911, 42, 1.

² Underhill, Wells, and Goldschmidt, Jour. exp. Med., 1913, 18, 317.

³ Post, Jour. Amer. Med. Assoc., 1914, 62, 592.

rate the alcohol from the extract. Dissolve the residue in dilute ammonium hydroxid, transfer to a test-tube, add a good-sized crystal of silver nitrate and heat gently. Tartaric acid is indicated by the formation of a silver mirror.

ETHER

Ether has but little toxicologic importance. The most frequent cause of death from ether has been its use as an anesthetic; the figures in various compilations of statistics have been from 1 death in 2500 to 1 in more than 50,000 anesthetizations. Perhaps 1 death in from 12,000 to 16,000 would represent an average. Acute ether intoxication by inhalation was quite common among the workers in some departments of smokeless powder factories during the World War¹; slight blood changes were found in some of those exposed for a considerable period to ether vapor. Ether has also been used as a means of committing suicide, and chronic poisoning has resulted from its use as an intoxicant. Serious accidents have resulted from ether vapor catching fire from free flames, x-ray machines, etc.

Properties.—Ether (Æther, U. S. P., sulphuric ether, ethyl oxid ($C_2H_5)_2O$) is a colorless liquid of peculiar penetrating odor and sweetish, pungent taste. It evaporates very rapidly, producing great cold. Pure ether has a specific gravity of 0.713, a boiling-point of 35° C. (95° F.), and a solidifying point of -129° C. (-200.2° F.), but commercial ether usually has a higher specific gravity and a higher boiling-point, for it contains alcohol (usually about 4 per cent.), and a little water. Ether is very inflammable and its vapor forms a highly explosive mixture with air. Ether is easily soluble in chloroform and alcohol, sparingly so in water. Spirits of ether (Hofmann's anodyne) is a mixture of 1 part ether with 3 parts alcohol.

The physiologic action of ether is, in the main, similar to that of alcohol, but it acts more promptly and the effects pass off more rapidly.

Symptoms.—The symptoms following the inhalation of ether are very similar to those due to chloroform, as already described. The vapor is irritating to the larynx and gives rise to a feeling of suffocation; the respiration and heart are slowed reflexly and rendered irregular. The secretion of mucus and of saliva is much increased. Sensation and consciousness are soon lost, and if too much ether is given, death results—usually from failure of the respiration²; in some cases, however, if the heart is diseased death may result from failure of the heart.³

When ether is swallowed there are an intense burning sensation in the throat and stomach and a rapid, intense intoxication, similar to, but of shorter duration than, that caused by alcohol. The irritation may lead to inflammation of the stomach and intestines. The ether is quickly volatilized in the stomach and the distention of this organ

¹ Hamilton and Minot, *Jour. Ind. Hyg.*, 1920, 2, 41.

² See, e. g., cases reported by Biddlecombe, *Brit. Med. Jour.*, 1892, i, 437; Herhold, *Berlin. klin. Woch.*, 1894, 31, 589.

³ See Hunt, *Lancet*, 1890, i, 588; Virchow's *Jahrb.*, 1892, i, 379.

may lead to discomfort and interference with respiration. Individuals may become habituated to the use of ether just as to alcohol, and be able to take large amounts without marked immediate effects; such a practice leads, however, to many nervous symptoms, such as trembling of hands, muscular weakness, cramps of the muscles, headaches, etc. This habit of ether-drinking has at times been quite common in parts of Ireland and other parts of Europe.¹ Occasionally a person acquires the habit of inhaling ether in order to secure the intoxicating effects.

Fatal Dose.—The fatal dose of ether when inhaled varies within very wide limits; it is largely a matter of the concentration of the vapor. It is necessary to maintain a concentration of about 6.7 per cent.² by volume of ether vapor (corresponding to a tension of about 49 mm. mercury) in the inspired air in order to maintain surgical anesthesia. A concentration of 9 per cent.³ has a distinctly depressing effect upon the medullary centers and 11.2 per cent.² causes respiratory paralysis in a few minutes in animals; the same relations almost certainly hold for man.⁴ The fatal dose when taken internally is not known; an individual recovered from 7 drams (26 c.c.). It is thought that 1 fluidounce (30 c.c.) would be fatal to most adults. Ether takers become accustomed to large amounts; there is a case reported in which a boy gradually learned to consume 2 pints (946 c.c.) of ether daily, taking part by inhalation, part internally.⁵

Fatal Period.—Death may occur at any stage of ether narcosis or before narcosis has been produced; or it may take place hours or days later from pneumonia.

Treatment.—In cases of arrest of breathing during ether anesthesia artificial respiration should be promptly practised. Strychnin, ammonia, or camphor may be given hypodermically as stimulants.

Postmortem appearances are not characteristic. There is usually hyperemia of the mucous membranes, and if the autopsy be made soon after death, the organs have an odor of ether.

Detection.—Owing to the great volatility of ether, its isolation from animal tissues is attended with some difficulty; in fact, the poison is likely to escape detection unless the attention of the analyst is specially directed to the substance by attendant circumstances.

A form of apparatus that is suitable for the distillation consists of an ordinary distilling flask, into which the material is to be introduced, provided with a cork, through which passes a long open glass tube

¹ Hart, *Brit. Med. Jour.*, 1890, ii, 885; cf. *Ibid.*, 1903, i, 98.

² This is the "uncorrected" figure found by Spenser (*Arch. exp. Path. u. Pharmacol.*, 1894, 33, 407) in experiments on cats and dogs; Spenser himself used the figure 3.4 obtained by actual analysis of the inspired air, but as Boothby (*Jour. Pharmacol. and Exp. Therap.*, 1914, 5, 379) pointed out the analyses were undoubtedly incorrect. The figure 6.7 per cent. agrees with that obtained by Boothby and also with that obtained by Dreser (*Arch. exp. Path. u. Pharmacol.*, 1895, 37, 384) for man; see also Ritschel and Stange, *Arch. int. de Pharmacol. et de Thér.*, 1913, 23, 191.

³ Spenser's "uncorrected" figure.

⁴ Compare Chloroform; also Boothby, *Jour. Amer. Med. Assoc.*, 1913, 61, 830.

⁵ Sedant, *Gaz. des Hôp.*, 1883, 56, 844.

drawn out at its lower end and bent upward. This tube should scarcely dip below the surface of the liquid in the flask, and serves to admit air at the end of the operation. The exit tube of the flask enters a Liebig's condenser which is connected by means of an adapter with a succession of three Pelligot tubes and a final U tube containing a little mercury. All connections should be made with well fitting corks (not rubber stoppers), and the system tested with a filter pump.

The material under investigation is placed in the flask, the Pelligot tubes surrounded with a mixture of ice and salt, and the amount of mercury in the valve so arranged that inward pressure will be relieved by the entrance of air into the flask through the long tube. Distillation is then carried on very slowly by means of a warm water-bath. The distillate, if obtained in quantity, is treated with fused calcium chlorid and submitted to a second distillation with all the precautions noted; but ordinarily the amount of ether recovered will be limited to a few drops that will be found in the first Pelligot tube. The tube

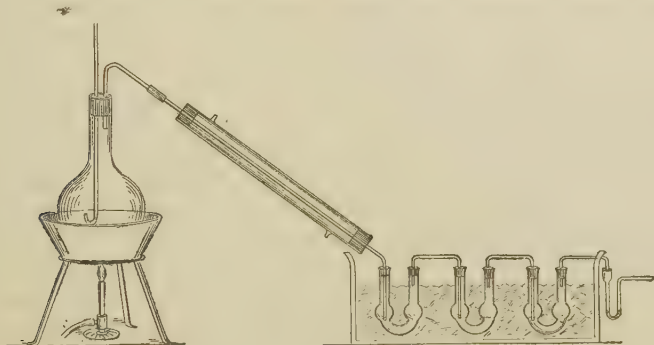


FIG. 64.—Apparatus for detecting ether.

is disconnected and closed with solid corks, one of which is provided with a slit carrying a small piece of filter-paper that has been moistened with a mixture of sulphuric acid and bichromate of potassium. In the presence of ether vapor the bichromate will be reduced to green chromium sulphate. This reaction in connection with the properties already noted (volatility, odor, combustibility) sufficiently identifies the substance.

AMYL NITRITE

Amyl nitrite (Amylis nitris, U. S. P., containing about 80 per cent. of $C_5H_{11}NO_2$) is a very volatile yellowish liquid with a peculiar, fruit-like odor. Its specific gravity is 0.877, and the boiling-point, $96^\circ C.$ ($204.8^\circ F.$). It is insoluble in water. It is given in medicine by inhalation to cause dilatation of the arteries. The chief symptoms are flushing of the face and upper parts of the body. After large doses vomiting, unconsciousness, and collapse, with shallow respiration and cyanosis, may occur. Curious disturbances of vision also result. In the lower animals amyl nitrite causes the blood to assume a chocolate

color, due to the formation of methemoglobin. The symptoms following the internal administration of amyl nitrite are similar to those caused by the inhalation of the drug. After doses of one teaspoonful,¹ a dessertspoonful,² and several grams³ the chief symptoms were great weakness, cyanosis, and a very feeble, rapid, then slow, intermittent pulse; spasmodic, irregular respiration, gastric irritation, and recovery under appropriate treatment (emetics, strychnin, and digitalis). Cadwallader⁴ reported a fatal case attributed to the inhalation of $\frac{1}{2}$ ounce of amyl nitrite.

Isolation.—By distillation without steam as outlined under alcohol. The receiver should be kept in an ice-bath. This aqueous solution can be used for the tests. If it is desired to isolate it further, the distillate is shaken out with ether. The ether is then allowed to evaporate at room temperature. Great care must be exercised in this, for the amyl nitrite very easily volatilizes.

Detection.—The above distillate is heated for some time with NaOH in a flask with a well-cooled reflux condenser. This process converts the amyl nitrite into amyl alcohol and NaNO_2 . The amyl alcohol is then tested as outlined under that substance. The nitrite is tested according to the well-known qualitative tests for that substance.

Amyl Acetate.—The action of amyl nitrite is largely due to the ONO group; another ester of amyl alcohol, viz., *amyl acetate* is extensively used in the shoe, jewelry, and other industries as a solvent for varnishes, lacquers, etc.; workmen frequently find the odor disagreeable and sometimes have an exaggerated idea of its dangers. While it may cause unpleasant effects the data at present available (summarized by Hamilton⁵) affords little evidence of its danger as an industrial poison. When taken internally, as an ingredient of a proprietary cough remedy, it caused very unpleasant symptoms suggestive of those of amyl nitrite.⁶

ETHYL BROMID

Ethyl bromid (hydrobromic ether, $\text{C}_2\text{H}_5\text{Br}$) is a heavy, colorless, very volatile liquid, with a chloroform-like odor. When inhaled, it produces anesthesia, or, rather, analgesia, with great rapidity. Consciousness returns within two or three minutes after the administration is discontinued. The rapidity with which the effects appear and pass off again has led to the somewhat extensive use of ethyl bromid, either alone or mixed with other anesthetics, for brief surgical operations, as in dentistry. Ten volumes percentage is necessary to anesthetize animals within five minutes, and if this concentration is maintained for fifteen minutes, death occurs: hence it cannot be considered as an

¹ Shoemaker, Medical News, 1893, 62, 544.

² Center, Indiana Med. Reporter, 1880, 1, 70.

³ Rosen, Centralbl. f. klin. Med., 1888, 9, 777.

⁴ Cadwallader, Med. Rec., 1896, 50, 816.

⁵ Hamilton, Jour. Amer. Med. Assoc., 1917, 69, 2037; cf. also Koelsch, Hyg. Rundschau, 1913, 23, 239.

⁶ Alexander, Jour. Amer. Med. Assoc., 1915, 64, 1348.

entirely safe anesthetic; the margin between an effective and a dangerous dose is very small. As a matter of fact, a number of deaths have occurred from its use. In a series of 60,000 cases there were 16 deaths, *i. e.*, 1 death in 3750. In another series there was 1 death in 5220 cases. In some of these cases death resulted from the long-continued administration of the anesthetic, a practice that does not seem to be justified for ethyl bromid has an even greater tendency to cause late poisoning than has chloroform.¹ Death may occur at any period of the administration, as within thirty seconds after the beginning,² or hours³ and days afterward.

Ethyl bromid readily undergoes decomposition; this change is indicated by the appearance of a yellow color. Such preparations are very poisonous, and some deaths have very probably been due to their employment. Death has also resulted from the use of ethylene bromid ($C_2H_4Br_2$); this substance, which is much more poisonous than ethyl bromid, having been dispensed instead of ethyl bromid.⁴ Several deaths have also resulted from the employment of ethyl bromid first and then of chloroform; in one of these cases death occurred seven days afterward with the symptoms of acute yellow atrophy of the liver.⁵

Isolation and Tests.—Ethyl bromid is sufficiently distinguished from other poisons containing bromin by its low boiling-point (38° – 40° C.— 100.4° – 104° F.), but owing to its instability, it is not likely to be recovered from the tissues. Ethylene bromid decomposes quantitatively when heated with zinc and a little water, producing zinc bromid and ethylene gas,⁶ $C_2H_4Br_2 + Zn = ZnBr_2 + C_2H_4$. The reaction may be performed with a very small quantity of material, and the gas shown to burn with a smoky flame.

ETHYL CHLORID

Ethyl chlorid (*Æthylis chloridum*, U. S. P.), which is used as a local anesthetic, has also been used as a general anesthetic for brief operations. It has many of the dangers of ethyl bromid and of chloroform; Glaister⁷ states that from 20 to 30 deaths have been reported from its use in England.

Properties.—At low temperatures or under pressure it is a colorless, mobile, very volatile liquid, with a characteristic ethereal odor and a burning taste. It is slightly soluble in water, freely soluble in alcohol and in ether. Its specific gravity at 0° C. (32° F.) is 0.921, and its

¹ Dreser, *Arch. exp. Path. u. Pharmacol.*, 1895, 36, 285.

² Simons case, *Phila. Med. Jour.*, 1899, 4, 367.

³ Sims, *Med. Rec.*, 1880, 17, 361.

⁴ Scherbatscheff, *Arch. f. exp. Path. u. Pharmacol.*, 1901, 47, 1. See also Hirsch, *Therap. Monat.*, 1888, 2, 556; Asch, 1889, 3, 385.

⁵ Reich, *Ibid.*, 1893, 7, 250.

⁶ Gladstone and Tribe, *Ber. d. deutsche chem. Gesell.*, vii, 365.

⁷ Glaister, *Med. Jurisp. and Toxicology*, 1915, 722; cf. Courtois-Suffit, *Jour. Amer. Med. Assoc.*, 1921, 76, 1117; Guedel, *Ibid.*, 1921, 77, 427, states that ethyl chlorid in overdose produces one of two sets of symptoms, which he designates as (1) the spasm type, and (2) the respiratory depression type. See also Jaeger, *Zentralbl. f. Chir.*, 1921, 48, 1073; Hofmann, *Münch. med. Wehnschr.*, 1922, 69, 159.

boiling-point is 12° to 13° C. (53.6° to 55.4° F.). It burns with a smoky, greenish flame, with the production of HCl, which may be detected in the usual manner.

NITROGLYCERIN

Many of the cases of poisoning by nitroglycerin are "industrial," and occur among workmen engaged in its manufacture or in the manufacture and use of dynamite and other high explosives; other cases are due to accident or to its use for the purpose of murder. In most of the cases of criminal poisoning the nitroglycerin has been added to alcoholic drinks. Some interesting testimony as to the use of nitroglycerin was given by a criminal.¹ He said: "The way to work it was to engage a boat on a warm day, entice the victim to go for a row, give him a drink of whisky dosed with nitroglycerin, and then set him adrift; when discovered dead, they would pronounce it a case of death from sunstroke." He had practised the use of different poisons on poor tramps in the slums of Chicago, and the nitroglycerin "was the surest and the best." He also said that a chemist could easily be deceived by it.

Properties.—Nitroglycerin (glyceryl trinitrate, or glonoin, $C_3H_5(NO_3)_3$) is a pale yellow, odorless, oily liquid that is nearly insoluble in water, soluble in absolute alcohol, ether, and chloroform. When heated above 250° C. (482° F.) it explodes. It will also explode violently on concussion. A 1 per cent. solution of nitroglycerin in alcohol is used in medicine under the name of Spiritus glycerylis nitratis (U. S. P.).

The **physiologic action** of nitroglycerin is similar to that of amyl nitrite, but its effect is more prolonged. It is an extremely active drug, the medicinal dose being from $\frac{1}{2}$ to 2 minims (0.03–0.1 c.c.) of the 1 per cent. solution; even these doses may cause such powerful pulsations of the heart that a pen held in the hand is visibly jerked.²

Symptoms.—The most marked symptom in the milder cases of poisoning is a very severe headache—the "powder headache" of those engaged in the manufacture of nitroglycerin,³ dynamite, ballastite, cordite, etc.; there may also be drowsiness and vomiting. The poisoning may result from the taking of the nitroglycerin internally or in the form of vapor, or it may be absorbed by the skin.⁴ A single drop rubbed into the skin may cause a headache lasting for ten hours; there may be a loss of vision; a maniacal condition may develop.⁵

When a large dose of nitroglycerin is taken internally, the chief symptoms are a burning sensation in the throat, vomiting, colicky pains, and sometimes diarrhea. The arteries of the head dilate and throb; the skin is flushed and perspiring; severe headache is almost invariably present, and dizziness and weakness follow. The respiration is at first accelerated, but it soon becomes dyspneic, cyanosis is marked,

¹ McVey, Boston Med. and Surg. Jour., 1894, 131, 458.

² Murrell, Lancet, 1879, i, 80.

³ Laws, Jour. Amer. Med. Assoc., 1898, 31, 793.

⁴ Evans, Jour. Amer. Med. Assoc., 1912, 58, 550.

⁵ Laws, Ibid., 1910, 54, 793; Ebright, Ibid., 1914, 62, 201.

and in prolonged cases some methemoglobin is probably formed. Coma develops, and death results from failure of the respiration. Delirium and clonic convulsions are sometimes observed.

Workmen in factories, as well as patients receiving the drug medicinally, rapidly acquire a tolerance for it; thus a case is reported in which a patient became accustomed, in the course of a year, to 6 grains (0.39 gm.) daily. There is, however, a chronic form of poisoning among those who handle nitroglycerin a great deal; among the effects are tachycardia on exertion and ulcers on the fingers and skin eruptions.

Fatal Dose and Period.—In most of the fatal cases a large amount of the poison was taken, but it seems probable that a very few drops would prove fatal— $\frac{1}{50}$ minim (0.001 c.c.) has produced most severe headache. Even after large doses death does not seem to have occurred for at least two hours; in other cases it was delayed for six hours or more.

Treatment.—The elimination of the poison should be hastened by washing out the stomach and by the administration of cathartics. In severe cases blood-letting, with subsequent saline transfusion, may be resorted to. Large quantities of black coffee seem to give great relief to the severe headaches.

The chief **postmortem appearances** are hyperemia of the stomach and intestines and also of the brain and its membranes. The mucous membrane of the air-passages may be of a reddish-brown color.

Isolation.—Owing to the unstable character of nitroglycerin in the presence of reducing agents and the close correspondence of its solubilities with those of the fats, the isolation of the substance from the tissues is attended with considerable difficulty. Moreover, Werber's experiments upon poisoned animals show that the poison is rapidly decomposed in the body and is not likely to be found in the urine, blood, or liver. The attention of the analyst should, therefore, be specially directed to the stomach contents, as well as to vomited matter, and any suspicious oil drops found in the digestive tract should be submitted to tests before purification.

Werber's method¹ of extracting nitroglycerin from the organic matter by direct treatment with chloroform or ether will, in many instances, yield satisfactory results; but owing to the great difficulty of removing the solvent after it has been thoroughly shaken with organic matter, the following procedure will often be found advisable. The material under examination is faintly acidified with sulphuric acid, and digested for twenty-four hours with five or six times its volume of absolute methyl alcohol. The solution is then filtered, most of the alcohol is driven off on the water-bath, and the residual fluid, which should not be filtered, is shaken out with ether or chloroform. Upon evaporation of the organic solvent nitroglycerin will remain as a viscous oil. Although the substance will be highly contaminated with fat, it is well to make a preliminary test at this point, and especially when the amount of material is small. On treatment with a small quantity of cold alcohol

¹ Ztschr. f. anal. Chem., vii, 158.

the nitroglycerin will pass easily into solution, leaving the fat, and may be thrown down as oil drops by the addition of a sufficient amount of water.

Tests.—1. Nitroglycerin explodes violently when heated in a capillary tube.

2. A tenth of a milligram of nitroglycerin may be shown by the purple-red color that is produced upon treatment with a trace of anilin or brucin and a drop of concentrated sulphuric acid.¹ The test is given also by nitrates, nitrites, and many nitro compounds.

3. The following reaction requires a great expenditure of material, but in the absence of fats, furnishes valuable evidence in the identification of nitroglycerin. The substance is evaporated on the water-bath with a strong aqueous solution of yellow ammonium sulphid. Glycerin and ammonium nitrite are formed²:



The pasty residue is extracted with alcohol, which, upon evaporation, leaves the glycerin. This may be identified by its sweet taste and by the odor of acrolein, which is produced when the substance is heated dry with acid potassium sulphate:



A second portion of the suspected substance is treated successively with yellow ammonium sulphid, an excess of lead carbonate, and a trace of lead acetate. After filtration the liquid is tested for a nitrite with metaphenylenediamin and sulphuric acid.

HYDROCYANIC ACID AND THE CYANIDS

Hydrocyanic acid and some of its salts are used very extensively in the arts, and to a very limited extent in medicine. They are readily accessible to the public. Hydrocyanic acid is also found very widely distributed in nature; it occurs, almost always, in more or less firm combination in many plants, and is contained in certain flavoring agents or liqueurs derived from such plants. It may be produced by bacterial action within the body, Pathy³ having shown its formation under the influence of *Bacillus pyocyaneus*.

The cyanids (hydrocyanic acid and its compounds) occupy a very prominent place in the list of poisons; in the statistics of some European countries they occupy the third or fourth place in the order of the frequency with which death is caused by poisons. Of the 1433 cases of fatal poisoning in England and Wales for the years 1912 to 1913, 166 were due to the cyanids.

The greater number of the cases of cyanid poisoning are due to suicide. Thus, of the 426 cases reported in England for the ten years ending in 1892, 344 cases were due to the use of the cyanids for suicidal

¹ Werber, *Loc. cit.*

² Bloxam, *Chemical News*, xlvii, 169.

³ *Jour. Inf. Dis.*, 1921, 29, 73.

purposes; 38 cases were due to accident or negligence, while in but 14 were they used for the purpose of murder. Of 166 fatal cases occurring in England and Wales in 1912 to 1913, 153 were suicidal and 13 accidental; of 135 cases reported in the registration area of the United States for 1909, 120 were suicidal and 15 accidental; of 30 fatal cases occurring in St. Louis, 1910 to 1914, 28 were suicidal and 2 accidental. In 793 poisoning cases of a criminal character in France occurring in the twenty-one years from 1851 to 1871, the cyanids were used in but 4. Witthaus¹ was able to find in the literature up to 1911 only 36 cases in which hydrocyanic acid and its compounds were alleged to have been used for purposes of murder.

In some statistics the greater number of cases were due to aqueous solutions of hydrocyanic acid itself; in others, to potassium cyanid. The former has been used most frequently for suicidal purposes by pharmacists, chemists, and physicians; the latter has been used chiefly by photographers and electroplaters. Poisoning with the various substances containing hydrocyanic acid (oil of bitter almonds, peach kernels, etc.) is not very common.

Hydrocyanic acid, generated by the action of an acid upon potassium or sodium cyanid, has been used in the United States since 1886 as an insecticide with but few accidents; the introduction of this practice into Germany has led to a number of deaths. The concentration of the gas in the air in this process is about 1 per cent. by volume.

Properties.—Hydrocyanic acid (hydrogen cyanid or prussic acid, HCN) is a colorless, transparent liquid of a penetrating characteristic odor resembling that of peach kernels. It boils at 26.5° C. (80° F.), and solidifies at -15° C. (5° F.). Even at temperatures below its boiling-point it volatilizes so rapidly that if a drop falls on a glass plate a portion of it freezes. The pure acid is very unstable and is rarely seen, even in the chemical laboratory. The only preparation of hydrocyanic acid recognized in the U. S. Pharmacopeia is a 2 per cent. solution—the *Acidum hydrocyanicum dilutum*; this is a colorless fluid with a characteristic odor and taste, and ought not to be kept long, as it is liable to decomposition. Much of the acid used in medicine has undergone partial decomposition, and is therefore under 2 per cent. in strength. HCN is contained in small amount in the U. S. P. preparations of wild cherry bark (*Prunus virginiana*), and (to the extent of 2 to 4 per cent.) in the *Oleum amygdalæ amaræ*, being derived from amygdalin.

Potassium cyanid (KCN) is a white, deliquescent salt, odorless when perfectly dry, but emitting the odor of hydrocyanic acid when moist. It is soluble in 2 parts of water. The solution has an alkaline reaction and decomposes slowly in the cold, and rapidly upon heating. Commercial preparations contain some cyanate and carbonate of the alkali. This salt, or the sodium salt² (which is in the U. S. P.), is used extensively in photography, in silver electroplating, in the gilding of

¹ Witthaus, *Manual of Toxicology*, 1911, 800.

² Most of the cyanid on the market at the present time is the sodium cyanid.

metals, in gold-mining, in the cleaning of gold and silver, and in the manufacture of certain dyes. In some of these processes hydrocyanic acid vapors are emitted, and these may give rise to poisoning. One part of hydrocyanic acid is contained in $2\frac{1}{2}$ parts of potassium cyanid; when the salt is taken into the stomach, hydrocyanic acid is slowly set free by the action of the acid of the gastric juice, so that the effects of potassium cyanid are practically the same as those of an equivalent amount of hydrocyanic acid; the salt, however, causes some corrosion at the point of application.

Physiologic Action.—When a solution of hydrocyanic acid is applied to the skin or to a mucous membrane, it causes numbness and a partial loss of sensation. Upon the central nervous system it acts first as a stimulant, causing excitement and then convulsions; the convulsions seem to be caused chiefly by the action of the poison upon the medulla and lower parts of the brain. The stage of stimulation is very brief, and is followed by paralysis of all parts of the central nervous system. The respiration is first stimulated and then paralyzed: the circulation is similarly affected. Hydrocyanic acid exercises a depressant action upon protoplasm in general: the movements and nutritive processes of both plants and animals are impaired by it. Geppert¹ showed that its effect upon protoplasm was due largely to its retarding oxidation processes; as a consequence of this action, the tissues are no longer capable of absorbing oxygen, and in the higher animals the blood, not giving up its oxygen to the tissues, retains its bright arterial color in the veins.

When hydrocyanic acid is added to drawn blood, the latter loses its power to decompose hydrogen dioxid: the blood also retains its red color much longer than does normal blood. Various combinations of hydrocyanic acid with the blood pigment have been described, but such combinations are not formed in the body during life. In cases of fatal poisoning, however, the dependent parts of the body often present a bright red color. The explanations offered for this are not entirely satisfactory.

Hydrocyanic acid is rapidly changed in the body: part forms sulphocyanids and is eliminated in the urine in this form.

Hydrocyanic acid is readily absorbed from all mucous membranes. Very severe cases of poisoning have resulted from the inhalation of its vapors² or from its absorption from external surfaces.

Symptoms.—The symptoms of hydrocyanic acid poisoning vary according to the size of the dose and the purity of the preparation taken, and also with the condition of the stomach, whether empty or containing food. The symptoms in cases of poisoning with potassium or sodium cyanid are identical with those of hydrocyanic acid, except that the course may be slightly more prolonged. When a large quantity of the acid is swallowed, the symptoms seem to begin immediately or within a very few seconds: they are rarely delayed for more than one or

¹ Geppert, *Zeitschr. f. klin. Med.*, 1888, xv, 208 and 307.

² Franklin case, *Lancet*, 1899, i, 43.

two minutes. The patient may utter a cry as for help, and then fall down insensible; the respiration is at first rapid and convulsive, but soon becomes extremely slow and gasping. Convulsions are common, but in some cases the patient staggers a few steps and then falls down and dies in five minutes or less without sound or convulsion.

In most cases, however, the course is somewhat more prolonged, and it is possible to recognize several stages. As the poison is swallowed there are an acrid harsh taste and a feeling of constriction in the throat. Other symptoms may not begin for several seconds or even minutes, and the patient may perform a number of conscious acts, such as walking across the room, rinsing the glass from which the poison was taken, or concealing the bottle or throwing it out of the window. As a rule, however, if a fatal dose has been taken, no voluntary acts of any importance are performed¹; the feeling of constriction in the throat is followed by salivation, nausea, and occasionally, though rarely, by vomiting; these are followed by anxiety, confusion, vertigo, and headache. There are unsteadiness of the gait and a feeling of stiffness of the lower jaw. There are palpitation of the heart and a feeling of constriction in the chest, and the respiration becomes first rapid, then slow and irregular. The inspirations are very short, the expirations greatly prolonged. The patient becomes unconscious, falls suddenly to the ground in convulsions not unlike those of epilepsy. The skin is covered with a cold sweat; the pupils are dilated and insensible to light; the eyes are glassy, staring, and very prominent, as in other cases of asphyxia. The mouth is covered with foam, which is sometimes blood-stained; the breath smells strongly of hydrocyanic acid. The pulse is at first rapid, but so weak that it can scarcely be felt. The convulsions may be general and lead to opisthotonos, or they may be confined to certain groups of muscles; thus there is often trismus. The hands are usually clenched. Involuntary evacuations of the feces and urine, also of the semen, may occur.

The convulsive stage is followed by that of depression and paralysis. The patient remains unconscious and then becomes comatose; the skin is usually cyanotic; the temperature falls; the heart is very feeble and irregular; there is complete abolition of the reflexes. The most marked symptoms, however, come from the respiration; this ceases for long intervals and then there is a short, gasping inspiration, followed by a very prolonged powerful expiration. A little later the respirations become very slow and shallow and finally cease. A few weak contractions of the heart may be noticed after the respiration has ceased. Occasionally the respiration is stertorous,² resembling that of apoplexy.³ Sometimes convulsions do not occur, although the course is somewhat prolonged.⁴

In less severe cases of cyanid poisoning in which the patient finally

¹ See, however, the remarkable case reported by Hickman, Case 3, below.

² Kelly, *Lancet*, 1879, ii, 831.

³ Kolipinski, *Maryland Med. Jour.*, 1898, xl, 24.

⁴ See Case 3.

recovers the early symptoms are as those described above; the patient falls to the ground insensible, convulsions follow, succeeded by the stage of paralysis, in which the respiration becomes slow and shallow. After a little the respiration begins to improve and the patient awakes; vomiting now frequently occurs. A feeling of constriction in the chest and weakness, causing an unsteady gait, headache, difficulty in speech, and drowsiness may continue for a few days; as a rule, however, recovery is rapid and complete. In Kolipinski's case¹ recovery was complete in twelve hours. In the often-quoted case of Dr. Arnold² the patient (Dr. Arnold) was unconscious for six hours. Before the return of full consciousness he had the most horrible sensation of impending suffocation. As soon as the first disposition to vomit was felt, consciousness was perfectly restored and there was a complete cessation of all the symptoms.

The mortality in cases of cyanid-poisoning is very great; thus, in a series of 364 cases the mortality was 79.4 per cent., and the series included many cases of slight poisoning.³ In a series of 40 cases the mortality was 95 per cent.⁴

Cyanid poisoning may result from the inhalation of the vapors of hydrocyanic acid⁵; the chief symptoms are a sensation of constriction of the chest, dizziness, vertigo, and insensibility. In one case there were disturbances of the vision.⁶ Hydrocyanic acid is fatal to animals in one-half to an hour when present to the extent of 0.3 to 0.12 mg. per liter of air.

After poisoning with potassium or sodium cyanid, especially if the salt contains much potassium or sodium carbonate, recovery is somewhat slower, as there is much corrosion of the mucous membranes of the throat and stomach. Vomiting is more frequent in poisoning with potassium or sodium cyanid than with hydrocyanic acid.

A form of chronic poisoning is stated to occur among gilders, photographers, and others who are engaged in the handling of hydrocyanic acid, potassium or sodium cyanid. The symptoms are stated to be headache, vertigo, paleness of the face, loss of appetite, offensive breath, and difficult respiration. Collins and Martland⁷ reported a case of chronic poisoning in a silver polisher in which the symptoms were scarcely distinguishable from those of an anterior poliomyelitis: paralysis of the limbs and muscular atrophy, but with a certain degree of recovery. Chronic poisoning by hydrocyanic acid does not, however, seem to be a frequent result of the long-continued exposure to the gas.⁸ An irritation of the skin of the face like acne rosacea is described.

The **diagnosis** of acute cyanid poisoning is usually easy; the odor

¹ Kolipinski, Loc. cit.

² Arnold, Amer. Jour. Med. Sci., 1869, 57, 104.

³ Witthaus, Loc. cit.

⁴ Lesser, Virchow's Archiv, 1881, 83, 198.

⁵ Tintemann, Deut. med. Woch., 1906, 32, 1703.

⁶ Tatham, Brit. Med. Jour., 1884, i, 409.

⁷ Collins and Martland, Jour. Nerv. and Ment. Dis., 1908, 35, 417.

⁸ Fühner, Deut. med. Woch., 1919, 65, 847; Koelsch, Zentralbl. f. Gewerbehyg., 1920, 8, 93, 101; Holtzmann, Ibid., 1921, 9, 44.

of the poison alone is often sufficient to make the diagnosis very probable. Brandy or other alcoholic beverages may, however, obscure the odor of the hydrocyanic acid.¹ If but a small dose of the cyanid has been taken, the symptoms may resemble those of nitrobenzene poisoning²; the symptoms in the latter case, however, are usually slow in appearing, and there is often marked cyanosis, which may continue for days.

Fatal Dose.—The smallest dose of hydrocyanic acid known to have caused the death of an adult seems to have been about $\frac{1}{2}$ dram (1.87 c.c.) of the 2 per cent. solution³; this corresponds to $\frac{6}{10}$ grain (0.04 gm.) of pure hydrocyanic acid. A healthy woman, aged twenty-two, died in fifteen to twenty minutes from about $\frac{9}{10}$ grain (0.058 gm.) contained in a lotion.⁴ In another case a man took a similar dose and was insensible for four hours, but recovered. From these cases it would seem that 1 grain (0.064 gm.) of hydrocyanic acid, corresponding to 50 minims (3 c.c.) of the 2 per cent. solution, is the smallest quantity that, under ordinary circumstances, would prove fatal. Similarly, 2.4 grains (0.154 gm.) may be regarded as the minimal fatal dose of potassium cyanid. In a number of cases 5 grains (0.32 gm.) have caused death. In nearly all fatal cases of cyanid poisoning much more than the lethal dose has been taken. Recovery has also frequently followed much larger doses, but in many cases it is uncertain just how much of the acid was actually taken, as the commercial preparations vary so greatly in strength. Thus recovery has followed $\frac{1}{2}$ ounce (15 c.c.) of the 2 per cent. solution⁵ (4.8 gr.—0.31 gm.—hydrocyanic acid) and even larger doses. Recovery followed the taking of what was estimated to be at least 20,⁶ 40,⁷ and even 50 or 60⁸ grains (1.2–3.84 gm.) of potassium cyanid. In most of these cases, however, the exact strength of the preparation was not determined.

Fatal Period.—Hydrocyanic acid is one of the most rapidly fatal poisons known, and in many cases of poisoning the victims have been found dead within a very short time after they had been seen perfectly well. The fatal period depends upon a number of circumstances; one of the most important of these is the amount of the poison taken. As a rule, if $\frac{1}{2}$ ounce (15 c.c.) or more of the 2 per cent. solution is taken, death occurs in from two to ten minutes. With smaller, but still fatal, doses life may be prolonged for some little time, but in most cases death occurs in less than half an hour. After 3 drams (11.1 c.c.) death occurred in twenty minutes⁹; after $\frac{1}{2}$ dram (1.87 c.c.), in one hour and twenty minutes.¹⁰ Probably by far the longest fatal period recorded is that in

¹ Howell-Thomas, *Lancet*, 1873, ii, 522.

² The case of "prussic acid" poisoning reported by Cox (*Indiana Med. Jour.*, 1902, 21, 156) is evidently a case of nitrobenzene poisoning.

³ Garstang, *Lancet*, 1888, ii, 15.

⁴ Case 2.

⁵ Case 1: Kolipinski, *Loc. cit.*

⁶ Higgins, *Medical Record*, 1891, xl, 687.

⁷ Ord, *Lancet*, 1886, ii, 1174.

⁸ Gillebrand, *Ibid.*, 1876, ii, 223.

⁹ Kelly, *Loc. cit.*

¹⁰ Garstang, *Loc. cit.*

which a suicide did not die for three hours and a half after taking an unknown amount of hydrocyanic acid.¹ In the great majority of cases recovery follows if the patient lives an hour.

Death may occur in potassium or sodium cyanid poisoning in as short a time as after hydrocyanic acid²; but, on the other hand, a few cases are reported in which death was delayed for several—*e. g.*, two—and even twenty-four hours.

Treatment.—In case the physician arrives before death occurs, he should wash out the stomach until the wash-water no longer has the odor of hydrocyanic acid. Some advise the addition of hydrogen peroxid or of potassium permanganate to the wash-water on the theory that these substances would convert the hydrocyanic acid into the relatively harmless oxamid, but it seems probable that this change takes place much too slowly to be of any help whatever. If the stomach-tube is not at hand, vomiting should be provoked by irritation of the pharynx or by household emetics; emetics, however, may fail entirely.³

A mixture of ferrous sulphate and magnesium oxid in water is said to be efficient⁴; the cyanid is converted into ferrocyanids which are only very slightly poisonous in the presence of an excess of alkali. Hot and cold douches may be employed to stimulate the respiration. In several cases life has apparently been saved by prompt recourse to artificial respiration.⁵ Hypodermic injections of atropin do not seem to have been of value. From experiments on animals it seems probable that hypodermic or intravenous injections of sodium thiosulphate would be of value⁶ if the amount of poison taken did not much exceed a fatal dose.

Postmortem Findings.—The most characteristic postmortem finding is the odor of hydrocyanic acid, which is noticed on opening the body; this odor is not marked, or may be absent if putrefaction has begun; it is said to persist longest in the cavity of the skull. A similar odor is noticed after nitrobenzene poisoning; the odor in the latter case, however, persists for some time when the organs are exposed

¹ Brit. Med. Jour., 1883, i, 131.

² Haskins, Boston Med. and Surg. Jour., 1870, lxxxii, 21. Three other cases of potassium cyanid poisoning are cited in this article.

³ Brit. Med. Jour., 1883, i, 131; Higgins, Medical Record, 1891, xl, 687.

⁴ Martin and O'Brien (Proc. Soc. Chem. Ind., Victoria, 1901, i, 119) recommend that in all mines and mining laboratories where opportunities for accidental poisoning by cyanids occur, solutions of ferrous sulphate and of caustic potash, and a small packet of magnesium oxid, together with a suitable receptacle for mixing and a stomach-tube, should be kept ready prepared in some suitable position so that they could be administered with only a few seconds' delay. The following are recommended to be prepared:

(1) 30 c.c. (1 oz.) of 23 per cent. solution of ferrous sulphate.

(2) 30 c.c. (1 oz.) of 5 per cent. solution of caustic potash.

(3) 2 gm. (30 gr.) of powdered magnesium oxid.

Nos. 1 and 2 should be kept in hermetically sealed tubes which can be broken into a receptacle and powdered magnesia and $\frac{1}{2}$ pint of water added, shaken up, and administered.

⁵ See Ord, Lancet, 1886, ii, 1174; Gillebrand, Ibid., 1876, ii, 223.

⁶ Lang, Arch. f. exper. Path. u. Pharm., 1895, xxxvi, 75; Hunt, Arch. int. Pharmacod. et de Thér., 1904, 12, 447. See, however, Flury and Heubner, Bioch. Zeitsch., 1919, 95, 249.

to the air, whereas that due to hydrocyanic acid rapidly disappears under these circumstances. The body often has the natural color of health, resembling that of sleep. The dependent parts of the body and the finger-nails¹ often show bright red or violet² patches, due probably to the formation of cyanmethemoglobin.³ The blood is generally fluid and dark. Hemorrhages are often found on the pleuræ and pericardium; the mucous membranes of the pharynx, esophagus, stomach, and duodenum may show marked injection or ecchymoses, although sometimes no abnormal appearances are noted. Frothy mucus is often found about the mouth and in the larynx and trachea; the jaws are usually firmly closed.

In some cases of potassium or sodium cyanid poisoning very characteristic lesions are found in the stomach.⁴ These are especially marked if the preparation contains much potassium or sodium carbonate. As is well known, potassium cyanid has a strongly alkaline reaction, and in a neutral or alkaline medium dissolves proteins and decomposes blood, just as does potassium hydroxid. The mucous membrane of the esophagus and stomach becomes swollen and is stained red⁵ or brownish-red by the cyanhematin that is formed by the combination of the hydrocyanic acid with the altered blood pigment. This appearance is not noted, however, if the contents of the stomach were acid when the poison was swallowed.

CASES OF POISONING BY HYDROCYANIC ACID

CASE 1.—A man, aged twenty-two, swallowed rather more than $\frac{1}{2}$ ounce of the fresh 2 per cent. solution of hydrocyanic acid, corresponding to 4.8 grains (0.31 gm.) of the anhydrous acid. He experienced a feeling of numbness and anesthesia of the lips, quickly followed by shortness of breath and loss of consciousness. When admitted to hospital shortly afterward, pupils were widely dilated, the right a little more so than the left; pulse 86, small and compressible; respirations shallow, and ranging between 40 and 50 a minute. No cyanosis; face had a rosy tint, but the surface was cold. Rectal temperature, 97.5° F. There was soon complete insensibility, with abolition of reflexes; pulse increased to 112 and became irregular. The dyspnea was extreme, but there was no pallor of the mucous membrane or lividity, the color continuing of the same bright arterial hue throughout. There was decided trismus, rendering the introduction of the stomach-tube difficult, and for a brief space there was rigidity of the limbs. There was involuntary escape of the urine.

The treatment consisted in thorough lavage of the stomach, the hypodermic injection of whisky, camphorated ether, strychnin and atropin sulphates, the administration of whisky and ammonia by the mouth, and the application of dry heat. Sugar, albumin, casts, leukocytes, epithelial cells, and oxalate of calcium crystals were found in the urine.

There were signs of returning consciousness in two hours after admission, and recovery was rapid.

Two drops of the portion of the acid remaining in the bottle found on the patient's person caused death in two and a half minutes when placed upon the tongue of a healthy kitten.⁶

CASE 2.—A woman, aged twenty-two, swallowed an ounce of a lotion containing $\frac{9}{10}$ to 1 grain of hydrocyanic acid. The patient, who was seated in a chair,

¹ Taylor, Brit. Med. Jour., 1892, ii, 1168.

² Richter, Prag. med. Wochenschr., 1894, xx, 105.

³ Kobert, Lehrb. der Intoxikationen, 1906, 849.

⁴ Von Hoffmann, Atlas of Legal Medicine (Saunders), Pl. 45 and 46, 1898; Lesser, Atl. d. ger. Med., Pl. 9; 10, f. 3; 14, f. 1.

⁵ Haskins, Loc. cit.

⁶ Shively, Amer. Jour. Med. Sci., n. s., 1890, c, 42.

instantly jumped up, ran the distance of a few feet, and then fell to the ground insensible. There were violent convulsions, the face was distorted, and the limbs were extended and fixed in tetanic spasm. After five minutes the limbs were still extended and inflexible, the face swollen and turgid, the lower jaw spasmodically fixed, the eyelids half closed, but the eye prominent and glistening, with pupil strongly dilated. She was foaming at the mouth, breathing at long intervals with a deep, inspiratory effort, and uttering a moaning noise; pulse imperceptible at wrist. She died quietly, without any further struggle, fifteen or twenty minutes after taking the medicine. The patient had not spoken after taking the poison; she did not scream, nor was she sick; feces and urine were not passed. Postmortem four days later; limbs still rigidly extended, fingers strongly clutched, countenance turgid and distorted, jaws fixed, eyes glassy and bright. The vessels of the brain and lungs were congested; the chest evolved a strong odor of hydrocyanic acid.¹

CASE 3.—A stout, muscular man, aged forty, drank by mistake $\frac{1}{2}$ ounce of a 1.48 per cent. solution of hydrocyanic acid. "The bottle was found replaced and the cupboard door put to, and it would seem that he had poured out his dose into a measure, and had drank it off standing at the cupboard; and, finding out his mistake, had put down the measure, and mechanically restoppered and replaced the bottle, closing the cupboard door, and had then run upstairs to the house surgeon, having on his way to cross the dispensary room, to open a spring door, to go up a crooked flight of fourteen steps, across a long landing, up a second flight of eighteen steps, and a distance of several more paces through two other doors into the house-surgeon's room." He told the house-surgeon that he had taken $\frac{1}{2}$ ounce of prussic acid and asked him to come to the basement; he then retraced his steps—a distance of from twenty-five to thirty paces and thirty-two steps. He stood in the middle of the room, moved his hand impatiently, and said: "Be quick—give me something." He drank some solution of ammonia and tincture of sesquichlorid of iron and tried to excite vomiting by putting his finger into his throat. After one or two abortive attempts at vomiting he fell suddenly, completely insensible. He died, without convulsions, in about ten minutes. "In a few hours after death the face regained its natural expression and color, and it was noticed that it had the hue of health, and perfectly resembled that of one asleep; but after the lapse of a few more hours it again became congested, red, puffed, and ecchymosed," and a little later face, scalp, neck, shoulders, and thighs were mottled deep red.

About 3.5 grains (0.22 gm.) of anhydrous acid had been taken.²

CYANOPHORIC GLUCOSIDS

A very long and ever-growing list of plants (over 180 species) contain, usually in minute amounts, amygdalin and other glucosids yielding, under certain conditions, HCN.³ Some of these have acquired considerable economic importance owing to numerous cases of poisoning of domestic animals to whom the plants or their products were fed. A number of cases of poisoning in man have resulted from such plants or from products prepared from them; cherry laurel distillate was well known as a toxic agent, often used for criminal purposes, long before HCN itself was discovered. The chief medicolegal interest at present in these substances arises from the probability that the defense in criminal cases will argue that HCN found by the prosecution came from substances eaten; hence the desirability of analysts using, as far as possible, strictly quantitative methods and having a knowledge of how much HCN may be derived from plants, or their parts, which might have been eaten. Lange⁴ gives the following figures for

¹ Letheby, *Lancet*, 1845, ii, 99; also 1845, i, 638.

² Hickman, *Lancet*, 1866, i, 310.

³ See, for example, Czapek, *Biochemie der Pflanzen*; Dunstan, Henry, and Auld, *Proc. Roy. Soc.*, London, 1907, 79B, 315; Armstrong, *Ibid.*, 360, various papers; Compton, *Chem. News*, 1912, 106, 163.

⁴ Lange, *Arb. Kais. Ges. Amt.*, 1907, 25, 478.

the amounts of amygdalin in some of the more common seeds: peach, 2.0 to 3.0 per cent. (= 0.11–0.16 per cent. HCN); plum and apricot, 1.0 per cent. (= 0.05 per cent. HCN); apple, 0.6 per cent. (= 0.03 per cent. HCN); cherry, 0.8 per cent. (= 0.04 per cent. HCN).

Amygdalin introduced into the body by itself is usually harmless, although mild symptoms of HCN poisoning have been reported from it; it is, however, frequently accompanied in nature by emulsin or other ferments which decompose it with the production of HCN according to the following equation:



Bitter Almonds.—Poisoning by eating bitter almonds themselves is comparatively rare, but a few fatal cases are on record.¹ Bitter almonds contain about 3 per cent. of amygdalin. Since amygdalin yields 5.9 per cent of hydrocyanic acid, somewhat more than 1 ounce (31 gm.) of the almonds would be required to yield 1 grain (0.064 gm.) of anhydrous hydrocyanic acid. Bitter almonds weigh on the average about 11 grains (0.7 gm.) each; hence death may be expected to follow the eating, by an adult, of about 50 almonds. Very severe symptoms were produced in a child by eating 10 bitter almonds; 12 to 15 bitter almonds caused dizziness, accelerated pulse, a cherry-red color of the face, spasm of the esophagus and pylorus, but recovery followed when the stomach was washed out with a solution of potassium permanganate (1 : 23,000) and magnesium sulphate was administered.² In a case reported by Maschka³ about 2½ ounces (77.5 gm.) were taken with suicidal intent. The symptoms began in a few minutes; there were unconsciousness and convulsions in ten minutes, and death in an hour and a half after the appearance of the first symptoms. Baker⁴ reports a case in which a man stated that he had eaten “two handfuls” of bitter almonds; the symptoms did not appear for some time, but were then very severe. Recovery followed. In another case (suicide) death resulted in two hours from a “handful” of bitter almonds.⁵

A few cases of severe, and even fatal, poisoning, especially in children, are reported from the eating of the kernels of the peach, the fruit of the common wild black cherry (*Prunus serotina*), the kernels of the common cherry and of the apple. The symptoms are due to the hydrocyanic acid, and are those already described; the course of the poisoning, however, is usually slow. Thus, a girl of five did not die for seventy hours after eating an unknown quantity of cherry kernels. A woman was severely poisoned, but recovered, after eating 20 apricot seeds.⁶ The bark and leaves also of many plants belonging to the plum family contain hydrocyanic acid in combination.

¹ Horrocks, Austral. Med. Gaz., 1898, xvii, 252.

² Blumenthal, Deut. med. Woch., 1919, xlv, 997.

³ See Blyth, Poisons, 4th ed., 1906, 220.

⁴ Baker, Brit. Med. Jour., 1881, ii, 12.

⁵ Ziemke, Münch. med. Woch., No. 24, 1905, 52, 1172.

⁶ S. Deak, Pester med. Chi. Press, No. 42, 1903, 1006.

Recently many cases of poisoning, especially in Germany and a few fatal cases in Porto Rico, have resulted from the eating of certain varieties of the bean *Phaseolus lunatus* (known commercially as Rangoon, Burma, Indian, Java, Moon, etc., beans). These beans contain a glucosid, phaseolunatin, from which hydrocyanic acid is liberated in the intestine. From 8 to 56 mgm. HCN may be obtained from 100 grams of the beans.¹ The symptoms have developed somewhat slowly and have consisted chiefly in vomiting, dizziness, and weakness. Beans containing any appreciable amount of HCN are not permitted entry into the United States.²

Oil of Bitter Almonds.—Far more serious than the above as a toxicologic agent is the oil of bitter almonds (*Oleum amygdalæ amaræ*, U. S. P.), a volatile oil obtained by distillation with water, from bitter almonds and other seeds containing amygdalin. The U. S. P. now requires that it shall contain not less than 85 per cent. of benzaldehyd and not less than 2 nor more than 4 per cent. hydrocyanic acid; part of the benzaldehyd is in loose chemical combination with HCN, forming benzaldehydecyanhydrin, but in the body the molecule is quickly and completely dissociated so that the toxicity of benzaldehydecyanhydrin corresponds closely to that of an equivalent amount of HCN.³

The crude oil of bitter almonds, which was formerly official, contained 2 to 14 per cent. HCN and was much used as a flavoring agent in confectionery, etc.; at present benzaldehyd or the "synthetic oil of bitter almonds,"⁴ which contains no hydrocyanic acid, is said to be largely used instead of the natural oil. The "essence of bitter almonds" is a solution of the oil in alcohol. Some pomades and salves contain oil of bitter almonds, and their use may lead to poisoning.

Of 492 cases of cyanic poisoning collected by Witthaus, 65 were due to the oil of bitter almonds; some of these were suicidal, others were accidental⁵; while in some cases the poison is alleged to have been used for criminal purposes.

The poisonous action of the oil of bitter almonds is due entirely to the hydrocyanic acid contained in it, and the symptoms are the same as those described above. In some cases, however, the effects are more slowly produced, although death may occur in ten minutes.⁶ The amount of hydrocyanic acid contained in the various specimens of the oil of bitter almonds varies considerably, so that it is impossible to state with accuracy the fatal dose; it is probable, however, that 10 drops of many preparations would be fatal. Taylor records a case in

¹ Sundendorf and Gahrzt, *Zeitsch. f. Untersuch. Nahr. u. Genussm.*, 1920, 38, 350; Dienemann, *Deut. med. Woch.*, 1920, 46, 1364.

² U. S. Dept. of Agr., Bur. of Chem. Serv. and Reg. Ann., No. 20, 1917.

³ Hunt, *Arch. int. de Pharmacol. et de Thér.*, 1904, 12, 447.

⁴ The "synthetic oil of bitter almonds" must be carefully distinguished from the "artificial or false oil of bitter almonds"; the latter is nitrobenzene and is very poisonous. Allen (*Internat. Med. Mag.*, 1893, 2, 126) described a case of poisoning by "oil of bitter almonds"; the intense and long-continued cyanosis and the "tar"-like character of the blood strongly suggest nitrobenzene.

⁵ Wright case, *Pharm. Jour. and Transactions*, 1883, 3 s., 13, pt. 2, 579, 619; 1883, 3 s., 14, pt. 1, 58.

⁶ Browning, *Lancet*, 1858, i, 128.

which a woman died in half an hour from 17 drops; in another case a man died in ten minutes from 2 drams (7.5 c.c.). On the other hand, with prompt treatment, patients have recovered from 6 drams (22.5 c.c.).

A child of three died in about two hours and a half after taking about 20 drops of the "essence of bitter almonds"; this should correspond to from $2\frac{1}{2}$ to 5 minims of the essential oil, but the preparations vary much in strength.

Cyanids Other than Hydrogen and Potassium Cyanids.—

All cyanids that are soluble in water or from which hydrocyanic acid is liberated by the action of weak acids are poisonous. Among such bodies may be mentioned the cyanids of sodium, ammonium, zinc, silver, and mercury. In cases of poisoning by mercuric cyanid the pathologic action of both mercury and hydrocyanic acid are noticed.

The double cyanids, such as potassium ferrocyanid, Prussian blue, Turnbull's blue, etc., are usually considered to be non-poisonous, but under some conditions hydrocyanic acid is split off and poisonous symptoms are produced.¹ Thus when potassium ferrocyanid is taken simultaneously with acids, fatal poisoning may occur.

Cyanic acid, the cyanates, and the sulphocyanates are nearly harmless. Cyanogen, cyanogen iodid, cyanogen chlorid, and nitroprussiate of soda² are all very poisonous.

Isolation.—There have been undoubted cases of poisoning with hydrocyanic acid where competent chemists were unable to detect the substance a few hours after its use. On the other hand, Dragendorff³ was successful in showing the presence of the poison in the stomach of a dog four weeks after the administration of potassium cyanid and in a human corpse eight days after death, while Struve's⁴ recovery of hydrocyanic acid from a mixture of potassium cyanid and organic matter that had been preserved in a closed vessel for five hundred and forty-seven days shows that a chemical examination should never be omitted where circumstances point to the use of the poison.⁵

In cases that have been embalmed (formalin) the hydrocyanic acid forms a condensation product with the formaldehyd (nitrile of oxyacetic acid); and this compound on distilling in acid solution does not yield HCN, but rather oxyacetic acid. Therefore it is possible to meet cases poisoned with cyanid in which the poison cannot be detected. Bischoff⁶ advises the analysis of the stomach, duodenum, blood, and organs rich in blood.

The separation of hydrocyanic acid from an acidified mixture of potassium cyanid and organic matter by distillation can offer no serious difficulty, but in case mercury or formaldehyd is present, hydrocyanic acid will not be found in the distillate. On the other hand, the presence

¹ See Huber, *Zeitschr. f. klin. Med.*, 1888, xiv, 515 (poisoning by Prussian blue; recovery).

² Hunt, *Arch. int. de Pharmaco. et de Thér.*, 1904, 12, 447.

³ *Ermittelung von Giften*, Göttingen, 1895, 70. See also Lewis, *Jour. S. African Assoc. Anal. Chem.*, 1921, 4, 19; *Chem. Abs.*, 1921, 15, 3431.

⁴ *Zeitschr. f. anal. Chem.*, 1873, xii, 14.

⁵ Sokoloff, *Ber. d. d. chem. Ges.*, 1876, ix, 1023.

⁶ *Ber. der Chem. Gesell.*, xvi, 1351.

of hydrocyanic acid in the distillate may be attributed to non-poisonous potassium ferrocyanid, potassium ferri cyanid, or potassium sulphocyanate,¹ all of which yield hydrocyanic acid under the conditions stated. Before proceeding with the distillation, therefore, a portion of the material is filtered or dialyzed, and the liquid is tested with an acidified mixture of ferrous sulphate and ferric chlorid. A blue color indicates either potassium ferrocyanid or potassium ferri cyanid, and a red color, potassium sulphocyanate. The result of this test, taken in connection with an analysis for mercury, will determine the course of the subsequent procedure.

In the absence of mercury and compound cyanids the material under examination is thoroughly macerated with water and the mixture acidified markedly with tartaric acid, and submitted to a slow distillation over a warm water-bath for five hours. Sokoloff's² contention that subsequent portions of the distillate contain more hydrocyanic acid than the first, and that the distillation should proceed for two or three days, has been shown by many chemists to be without foundation.³ In order to facilitate the escape of hydrocyanic acid a gentle current of air⁴ is passed through the material undergoing distillation and through a 2 per cent. solution of caustic potash, which is placed in the receiver for the absorption of the acid. The slight advantage of a current of carbon dioxid in preventing any oxidation of hydrocyanic acid to carbon dioxid and ammonia is more than counterbalanced by the expulsion of hydrocyanic acid from the distillate, which is sure to occur when the caustic potash contained in the receiver has become saturated with carbon dioxid.⁵ The distillate will contain potassium cyanid and caustic potash, and should be used for the tests given below directly or after neutralization, according to the requirements of the test in question.

In the presence of compound cyanids the suspected material is thoroughly macerated with a solution of sodium bicarbonate and submitted to a slow distillation. It is immaterial whether the mixture under examination is originally acid, alkaline, or neutral, since a perfectly definite condition of acidity is necessarily brought about by the presence of the bicarbonate. Upon gentle warming carbon dioxid is slowly evolved, and any potassium cyanid will be decomposed, giving off hydrocyanic acid, while the compound cyanids do not yield a trace of hydrocyanic acid under these conditions.⁶

For reasons already stated it is preferable in this instance to absorb the hydrocyanic acid in a dilute solution of silver nitrate that has been faintly acidified with nitric acid.⁷ The hydrocyanic acid is precipitated quantitatively as silver cyanid. The precipitate is filtered off, washed,

¹ Struve, Loc. cit.

² Sokoloff, Loc. cit.

³ Dragendorff, *Ermittlung von Giften*, Göttingen, 1895, 71; Bischoff, *Ber. d. d. chem. Ges.*, 1883, xvi, 1351.

⁴ Almen, *Zeitschr. f. anal. Chem.*, 1872, xi, 360.

⁵ Struve, Loc. cit.

⁶ Autenrieth, *Arch. d. Pharm.*, 1893, ccxxi, 107; *Ber. d. d. chem. Ges.*, 1893, 26, Ref., 727; Nandin and Montholon, *Ibid.*, 1876, ix, 1433.

⁷ Jacquemin, *Ann. de chim. et de Phys.* (5), iv, 139.

suspended in water, and decomposed with hydrochloric acid.¹ After filtering off the silver chlorid the fluid is neutralized with caustic potash and submitted to tests that are not vitiated by the presence of potassium chlorid. In case poisoning has been accomplished with mercuric cyanid it is necessary to decompose this compound by the addition of a little sulphuretted hydrogen water before the distillation is undertaken, and the employment or omission of sodium bicarbonate is determined by the presence or absence of double cyanids.² The use of silver nitrate in this case for the absorption of hydrocyanic acid is, of course, inadmissible. Beckurts' method³ of removing mercuric cyanid directly from the tissues with ether offers serious experimental difficulties.

An alternative method for affecting a separation of the double cyanids from the alkaline cyanids is the following: The suspected material is acidified with sulphuric acid. Now add enough FeCl_3 or FeSO_4 to precipitate completely the potassium ferrocyanid or the potassium ferricyanid respectively. Avoid great excess, because this may react with some of the alkali cyanids. This mixture is now filtered, to the filtrate is added enough potassium tartrate to take care of all the free sulphuric acid, and this is then distilled in the usual manner.

The nitroprussids are important in toxicologic investigations. They are poisonous if injected subcutaneously, breaking up into nitrite and sulphocyanate. These should be tested for in the urine. The soluble nitroprussid is extracted from tissue by means of water, and tested with alkaline sulphid solution. Distilling in acid media nitroprussid does not give off HCN. With sodium bicarbonate and heat it decomposes into hydrocyanic acid, sodium ferrocyanid, and ferric hydroxid.

Tests.—1. A portion of the suspected fluid, which may be alkaline or neutral, is treated with a small quantity of a freshly prepared mixture of ferrous sulphate and ferric chlorid. Unless the material was originally alkaline, a drop or two of caustic soda is now added and the solution is warmed. Upon acidification with hydrochloric acid Prussian blue is immediately precipitated. The reaction as described will show the presence of hydrocyanic acid in a dilution of 1 : 50,000.⁴

2. A few drops of the fluid are made alkaline⁵ if necessary and evaporated to dryness in a porcelain dish with a small quantity of yellow ammonium sulphid. The residue is taken up in a small quantity of very dilute hydrochloric acid; the solution is immediately filtered and treated with a trace of ferric chlorid. The red color thus produced⁶ is due to the formation of ferric sulphocyanate and serves for the detection of hydrocyanic acid in a dilution of 1 : 4,000,000.⁷ It is possible

¹ Bechamp, *Jahresb. d. Chem.*, 1853, 680.

² Autenrieth, *Loc. cit.*

³ *Arch. d. Pharm.*, cxxi, 576.

⁴ Link and Mockel, *Zeitschr. f. anal. Chem.*, xvii, 455; Almén, *Ibid.*, xi, 360; Carey Lea, *Amer. Jour. Sci.*, 1875, 122.

⁵ Almen, *Loc. cit.*

⁶ Liebig, *Liebig's Annalen*, lxi, 126.

⁷ Link and Mockel, *Loc. cit.*

for this test to yield a positive result where other tests for hydrocyanic acid fail. In such a case the red color is probably attributable to the presence of sulphocyanic acid originally in the distillate, and a second test should be made without using ammonium sulphid.¹

3. The suspected fluid is treated in turn with a dilute solution of potassium nitrite, a trace of ferric chlorid, and a sufficient amount of dilute sulphuric acid to produce a yellow color. The mixture is warmed, cooled again, and the excess of iron is precipitated with ammonia. The fluid will contain potassium nitroprussiate, which can be recognized by the violet color produced upon the addition of ammonium sulphid. Vortman claims as the limit to the sensitiveness of this reaction a dilution of 1 : 312,000.²

4. Ten milligrams of ferrous ammonium sulphate, and 10 centigrams of uranium acetate or cobalt nitrate are dissolved in 50 c.c. of water. One c.c. of the reagent is placed on a white porcelain surface, and a drop of the suspected solution, which should be neutral, is added. In case a cyanid is present, a purple color or a purple precipitate will result.³

5. The following test, which was first accurately described by Schonbein,⁴ is usually applied to suspected organic matter before any attempt is made to isolate the poison by distillation. The material under examination is placed in a small flask and acidified with tartaric acid. The mouth of the flask is closed by a tightly fitting cork whose lower surface is provided with a slit into which is inserted a piece of filter-paper that has been wet in turn with 5 per cent. tincture of guaiacum, and 0.1 per cent. copper sulphate solution. Almost immediately in a warm place the filter-paper assumes a fine deep blue color if hydrocyanic acid is present. The sensitiveness of the reaction is such⁵ that one can scarcely expect to show hydrocyanic acid when this test fails, but the blue color is produced by a comparatively large number of substances,⁶ among others chlorin, bromin, nitric fumes, ozone, and ammonia.

6. On treatment with silver nitrate and nitric acid soluble cyanids yield a precipitate of silver cyanid, easily soluble in ammonia or sodium thiosulphate. Under favorable conditions the precipitate will consist of clusters of radially concentric needles. When such is not the case, the substance can be distinguished from silver chlorid as follows: The precipitate is filtered off, washed with alcohol and ether, and placed in a narrow, dry test-tube with a little iodine. On gently heating, cyanogen iodid sublimes and is deposited on the cold part of the tube in beautiful pale red crystals.⁷

7. To a little of the suspected fluid are now added a few drops of

¹ Struve, Loc. cit.

² Monatsh. f. Chem., vii, 416.

³ Carey Lea, Loc. cit.; Jahresb. der Chem., 1875, 964.

⁴ Jour. f. prak. Chem., cvi, 263.

⁵ Almen, Loc. cit.; Link and Möckel, Loc. cit.

⁶ Struve, Loc. cit.

⁷ Blyth, Poisons, London, 1895, 205.

alkaline colorless reduced phenolphthalein solution, and then a little copper sulphate solution (1 : 2000). If cyanid is present a red color develops.¹ Oxidizing agents, as FeCl_3 , H_2O_2 , HNO_3 , will not react in this manner. Sensitive to 1 : 500,000.

8. To a little of the suspected solution are added a few drops of sodium picrate solution. On warming, a red color develops. In 1 per cent. solution the color develops rapidly. In more dilute solutions it requires a longer time. In a dilution of 1 : 1600 it appears only after twelve hours. Alkalis and acids interfere with the reaction.²

9. A little starch paste or a strip of starch-paper, made just slightly blue with a trace of iodine, will be decolorized at once by a trace of cyanid³ (1 : 1,000,000). This test is extremely sensitive, but not specific. Substances like hydrogen sulphid, carbon bisulphid, sulphur dioxide, uric acid, albumin, and alkalis will also decolorize.

10. For detecting cyanid in blood the following procedure is recommended by Kobert⁴: Two small bottles are filled, one with normal, the other with the suspected blood, both diluted (1 : 100). Both of these exhibit the absorption bands of oxyhemoglobin. The two bottles are now corked up air-tight and placed in a warm dark place for twenty-four hours or more. During this interval the normal blood has become darker in color, due to self-reduction, now yielding absorption bands of reduced hemoglobin. If the suspected blood also darkens and now gives absorption bands of reduced hemoglobin, no cyanid was originally present. But if the suspected blood remains bright red and still gives the absorption bands of oxyhemoglobin, then cyanid was originally present.



FIG. 65.—Crystals of silver cyanid from very weak hydrocyanic acid; $\times 340$.

11. Dilute both normal blood and the suspected blood (1 : 100); to each add some *neutral* hydrogen peroxid (avoid excess). The normal blood retains its red color and its oxyhemoglobin absorption bands. The cyanid blood changes in color from red to brownish red, brown, yellow, and finally white. Spectroscopically observed during these color changes, the absorption bands of the oxyhemoglobin are changed into those of methemoglobin, and these finally disappear, leaving no absorption bands at all.⁵

12. To a small quantity of a 1 to 4 per cent. aqueous solution of

¹ F. Weehuizen, Chem. Centralbl., 1905, 1191.

² C. Reichardt, Chemiker Zeitung, 1901, 25, 537.

³ R. Kobert, Stuttgart, 1891 (Über Cyanniet hämoglobin u. den nachweis der Blausäure).

⁴ Ibid.

⁵ Schönbein, Zeitschr. f. Biologie, 1867, 3, 325.

blood is added a trace of a dilute solution of potassium ferrieyanid. The color changes to brown, and the solution shows the well-known absorption spectrum of methemoglobin. Upon the addition of a drop of a neutral solution of a cyanid the color becomes bright red and the spectrum of methemoglobin disappears.¹

If cyanid is found present it may be of importance to decide whether it was taken as the potassium, sodium, or ammonium salt. The material is dialyzed for several hours. The dialysate is treated with silver sulphate until all the cyanid is precipitated. The AgCN is filtered off. In the filtrate the K^+ , Na^+ , and NH^4 are tested for according to well-known methods found in books on qualitative inorganic analysis. Quantitative determination of the basic element may be made upon the ash from the organs or gastric contents.

Estimation.—1. The solution in which hydrocyanic acid is to be determined is treated with 5 c.c. of strong ammonia and 2 c.c. of a 5 per cent. solution of potassium iodid.² Tenth-normal silver nitrate solution is added from a buret a drop at a time, and with continual stirring. At the appearance of a permanent cloud in the liquid the addition of silver nitrate is discontinued.³ One c.c. of tenth-normal silver nitrate corresponds to 0.005396 gram of hydrocyanic acid:



2. In the gravimetric determination of hydrocyanic acid the material is distilled over borax to remove traces of chlorin, and the distillate is treated with an excess of a dilute solution of silver nitrate that contains a trace of nitric acid. The precipitated silver cyanid is collected on a weighed filter, thoroughly washed, dried at 100°C . (212°F .), and weighed.

3. To avoid interference by other volatile substances Maisel suggests distilling in a sodium bicarbonate solution, and collecting through a well-cooled condenser into a freshly prepared solution of potassium sulphid. The excess potassium sulphid in the distillate is then decomposed with lead acetate, and filtered off. The filtrate is acidified with nitric acid; ferric sulphate is added, and the potassium sulphocyanid is titrated with N/10 silver nitrate (J. Volhard).

Oil of Bitter Almonds.—An ethereal oil, which on hydrolysis yields hydrocyanic acid, benzaldehyd, and glucose. On distillation, therefore, both the cyanid and the benzaldehyd must be tested for. The cyanid comes over in the first part of the distillate, the benzaldehyd a little later, yielding a milky distillate.

Benzaldehyd ($\text{C}_6\text{H}_5\text{CHO}$), (Benzaldehydum, U. S. P.).—**Properties.**—It is a colorless liquid when pure, boiling at 180°C . (356°F .), and having a characteristic odor. It gives all the ordinary aldehyd reactions. On oxidation it yields benzoic acid, and on reduction benzyl alcohol.

¹ Kobert, Lehrbuch der Intoxikationen, Stuttgart, 1893, 518.

² Denigès, Ann. de chim. et de phys. (7), vi, 381; Shurwood, Jour. Amer. Chem. Soc., xix, 400.

³ See also Gregory, Zeitschr. f. anal. Chem., xxxiii, 30.

Isolation.—The finely divided tissue is subjected to steam distillation in the usual manner. The distillate is extracted with ether in a separatory funnel. The ether layer is allowed to evaporate spontaneously, leaving the benzaldehyd as an oily residue.

Tests.—1. The characteristic odor.

2. In a flask with a reflux condenser oxidize some of the benzaldehyd to benzoic acid by means of sulphuric acid and potassium dichromate. When oxidation is complete dilute and distill with steam. Extract the distillate with ether. Allow the ether to evaporate. Characteristic crystals of benzoic acid, melting at 120° C. (248° F.), proves the presence of benzaldehyd in the suspected material.

3. To 1 c.c. of the distillate, or of suspected material, add 2 c.c. concentrated sulphuric acid and 2 drops of phenol, and then boil. A deep red color is produced. Cool and add 10 c.c. of water and make it alkaline with KOH. This changes the color to a blue-violet. If this is now acidified and extracted with ether, the color passes to the ether layer.

Oil of bitter almonds may be easily distinguished from nitrobenzene by heating on the water-bath for a little time with manganese dioxide and sulphuric acid; bitter almond oil treated in this way loses its odor; nitrobenzene is unaltered.

Estimation.—The benzaldehyd is completely converted to benzoic acid as described in the second qualitative test. The benzoic acid is extracted quantitatively with ether; the ether evaporated carefully. The crystalline residue of benzoic acid is repurified, dried, and weighed.

BENZENE

Benzene ("benzol," "crystallizable benzol," "coal-tar benzol," C_6H_6) is a hydrocarbon obtained from coal-tar by distillation; it is a light (specific gravity 0.881), colorless, refractive, very inflammable liquid, insoluble in water and boiling at 80.5° C. (176.9° F.). When benzene is taken internally, or when its vapors are inhaled in sufficient concentration, a condition of narcosis is produced; at the same time there is a stimulation of parts of the central nervous system leading to muscular tremor and convulsions. Its narcotic action is about as great as that of chloroform.¹

Poisoning may result from its oral ingestion for suicidal purposes or from its medicinal use; or, more frequently, it results from the inhalation of the vapors; the latter form of poisoning occurs chiefly in the industries,² especially in those in which benzene is extensively used as a solvent, as in rubber works.

When taken by mouth there is a burning sensation in the stomach, dizziness, flushing, restlessness, excitement, dilated pupils, fever, hallucinations and delirium followed in many cases by convulsions, or a condition of narcosis and coma and death from respiratory failure. Nine to 12 grams have caused serious collapse and a woman died in twelve

¹ Fühner, *Biochem. Zeitsch.*, 1921, 115, 235.

² See Hamilton, *Jour. Amer. Med. Assoc.*, 1922, 78, 627.

hours after swallowing about 1 ounce (30 c.c.) of nearly pure benzene.¹ When the vapors are inhaled in high concentration, as when it is spilled or workmen are endeavoring to stop a leak in a pipe, or when they enter a tank or still to clean or repair it, there may be almost immediate unconsciousness² and death may result in a few minutes; in less severe cases³ the symptoms are dizziness, flushing, roaring in the ears, a condition resembling alcoholic intoxication and unconsciousness. In the treatment artificial respiration may be necessary.

Postmortem Appearances.—The blood has usually been found fluid and there are often small hemorrhages in various organs.⁴

The most frequent form of poisoning is the chronic or subacute; cases of this character have been reported from industries in which benzene was used as a solvent for rubber.⁵ The symptoms in severe cases have been headache, purpuric eruptions ("purples"), hemorrhages from the gums and nose, listlessness, stupor, a very marked diminution in the number of the white blood-cells, an anemia of the aplastic type, fever, very rapid heart, and sometimes death several days after removal from the atmosphere containing the benzene. The blood of such cases just before death may show a red count of 600,000 to 800,000, a white count of 500 to 1100, and hemoglobin 8 to 29. Lymphocytes and large mononuclears may make up more than 50 per cent. of the white cells. The mortality in such cases has been very high. Blood transfusion seems to be the best treatment.

In mild cases of poisoning the first and sometimes the only effect observed has been the low white cell count (down to 1200 for example).⁶

These toxic effects are attributed to destruction of leukocytes and damage of the bone-marrow, lymph-glands, spleen, the whole hematopoietic system, and of the capillaries; in animal experiments the production of antibodies was diminished⁷ and the lighting up of latent infectious processes has been described.⁸

The marked effect of benzene upon the white blood-cells led to the use of benzene in the treatment of leukemia and also of polycythemia; disturbances of metabolism⁹ and extensive liver necroses¹⁰ have been reported from such use. Death has occurred some time after discontinuing the treatment.¹¹

¹ Kelynack, *Gaz. méd. de Paris*, 1893, 541; also *Med. Chronicle*, 1893-94, 19, 112.

² Heffter, *Deut. med. Woch.*, 1915, 41, 182; Hamilton, *Jour. Ind. Hyg.*, 1919, 1, 200.

³ Compare Beisele, *Münch. med. Woch.*, 1912, 59, 2286; Adamkiewicz, *Deut. med. Woch.*, 1920, 46, 1171.

⁴ Heffter, *Loc. cit.*

⁵ Santesson, *Arch. f. Hygiene*, 1897, 31, 336; Skand, *Arch. f. Physiol.*, 1900, 10, 1; Selling, *Johns Hop. Hosp. Bull.*, 1910, 21, 33; Monographs J. H. H. No. 2, 1912; McClure, *Jour. Amer. Med. Assoc.*, 1916, 67, 793; Harrington, *Boston Med. and Surg. Jour.*, 1917, 177, 203; Legge, *Jour. Ind. Hyg.*, 1920, 1, 539.

⁶ Newton, *Jour. Amer. Med. Assoc.*, 1920, 74, 1149.

⁷ Hektoen, *Jour. Infec. Dis.*, 1916, 19, 69.

⁸ Weisskotten, Schwartz, and Steensland, *Jour. Med. Res.*, 1915, xxxiii, 127; 1916-17, xxv, 63 and 71; 1917-18, xxxvii, 215; 1918-19, xxxix, 485; Weisskotten, Gibbs, Boggs, and Templeton, *Ibid.*, 1919-20, xli, 425.

⁹ Sohn, *Wien. klin. Woch.*, 1913, 26, 573.

¹⁰ Mühlmann, *Deut. med. Woch.*, 1913, 39, 2083.

¹¹ Spiegler, *Wien. klin. Woch.*, 1914, 27, 458.

Isolation, Quantitative Estimation, and Tests.—About 400 grams of tissue are ground up (while in frozen condition) and placed in a distilling flask. To this, 400 c.c. of water are added, thoroughly mixed, and acidified with a few drops of sulphuric acid. The flask is then connected with a long condenser, the distant end of which is immersed in about 25 c.c. of CCl_4 in an Erlenmeyer flask, serving as the receiver. A fast circulation of cold water through the condenser is maintained throughout the distillation, which should last for at least a half hour. The distillate, which consists of the CCl_4 layer and the aqueous layer, is then placed into a separatory funnel and well shaken for a few minutes and allowed to stand. When the two layers have separated, the lower one (CCl_4), which contains most of the benzene, is placed in a clean, dry flask and stoppered. The aqueous layer is shaken out in a similar manner three or four times, using fresh CCl_4 each time. These three portions are added to the first CCl_4 portion in the flask and contain practically all of the benzene. The entire amount of benzene in solution in this CCl_4 is about 60 to 100 mgs. To this tetrachlorid solution of the benzene is added about 10 c.c. of a 2 : 1 mixture of fuming nitric-sulphuric acid, and thoroughly shaken. This process converts the benzene to dinitrobenzene and mononitrobenzene. The whole mixture is placed in an evaporating dish and the CCl_4 carefully evaporated on the water-bath. The residue consisting of the nitrobenzene and the nitrating acids are allowed to cool and are then treated with about 50 c.c. of water. This is extracted several times with fresh portions of ether in a separatory funnel. The ether takes up all the nitrobenzenes and, on evaporating off the ether, the nitrobenzenes are left as a yellow residue with the characteristic nitrobenzene odor, and, on standing, yield the typical crystals. The nitrobenzene residue is weighed, and from this the amount of benzene originally present in the organ is calculated.

After determining its weight, the residue is used for further confirmatory tests. A small portion of it (about one-fifth) is taken up in about 5 c.c. of absolute alcohol and made alkaline with 3 drops of 30 per cent. sodium hydroxid. To this is added twice the volume of 1 per cent. fructose solution; an intense violet color results, then gradually fades. The remainder of the residue is taken up with about 10 c.c. of water in a test-tube. To this is added about 2 grams of zinc dust and concentrated hydrochloric acid, drop by drop, until a fair reaction (not too violent) ensues. If the mixture gets too hot, cool by immersing the test-tube in cold water. This reduction is continued for about ten minutes and results in the production of anilin and phenyl diamin. A portion of the reduced material is made alkaline with alcoholic sodium hydroxid, 1 drop of chloroform added, and the mixture is slightly heated. The typical disagreeable, irritating odor of isonitrile is easily perceptible. To another and major portion of the mixed amines, a few drops of 10 per cent. NaNO_2 (to diaotize) are added, then sodium carbonate solution until the first precipitate forms (ZnCO_3), then add 3 c.c. of 0.1 per cent. alkaline solution of beta-naphthol; an intense red-

brown color is obtained (delicate to 1 : 100,000). This test is more delicate than the fructose test, but it is not as specific.

NAPHTHALENE

Naphthalene (naphthalin, $C_{10}H_8$) is a hydrocarbon obtained from coal-tar. It is extensively used in the manufacture of dyes and as a repellant to moths; it has been used to a limited extent in medicine as a dusting powder, as an intestinal antiseptic, and as a vermifuge.

It is a white crystalline mass, insoluble in water, but soluble in alcohol, chloroform, ether, and oils; melts at $80^\circ C.$ ($176^\circ F.$), and boils at $217.2^\circ C.$ ($422.96^\circ F.$). It is moderately volatile at ordinary temperature, and poisoning has resulted from the inhalation of its vapors; thus persons sleeping under bedclothing dusted with naphthalene as a moth powder have suffered from loss of appetite, headache, and eczema.¹ Several cases of poisoning are reported in children who had eaten moth balls,² and in persons to whom it had been administered as a vermifuge,³ or as an intestinal antiseptic in typhoid fever,⁴ or as an application to wounds.⁵ The symptoms from the inhalation of the vapors have been chiefly malaise, headache, and vomiting; taken internally it has caused symptoms on the part of the central nervous system consisting in a staggering gait and dulness, and suggestive of alcoholic intoxication⁶; also gastric irritation with vomiting and abdominal pain; also symptoms on the part of the urinary organs: a burning sensation in the urethra, pain in the bladder and kidney region, and occasionally strangury. The urine may be dark brown, or become so on standing, from the presence of oxidation products of the drug; albumin and hemoglobin may be found in the urine; acute nephritis and jaundice have been reported.⁷

Cataract may be produced in the eyes of lower animals by the administration of naphthalin; also degenerative changes in the retina, etc.⁸ Similar effects have been described in man.⁹

The fatal dose is not known; a boy of six died after taking, in two days, 1.75 gm.¹⁰

The treatment consists in washing out the stomach and the administration of purgatives, since the drug is absorbed slowly; fats and castor oil, which dissolve the drug, should be avoided.

Tests and Detection.—Naphthalin may be isolated by distillation with steam, and extracting the distillate with ether. The ethereal solution forms with picric acid a yellow crystalline compound; 0.1 gram

¹ Evers, Berl. klin. Woch., 1884, 42, 593.

² Zangerle, Therap. Monatsh., 1899, 13, 122; Nash, Brit. Med. Jour., 1903, i, 251.

³ Prochownik, Therap. Monatsh., 1911, 25, 489; Heine, Med. Klinik, 1913, 9, 62; cf. Kaminer, Zeitsch. f. ärztl. Fortbild., 1920, 17, 647.

⁴ Götze, Berl. klin. Woch., 1884, 42, 666.

⁵ Frommüller, Memorabilien, 1883, 5, 257.

⁶ Zangerle, Loc. cit.

⁷ Heine, Loc. cit.; Lewin, Nebenwirkungen der Arzneimittel, 1899, 541; Nash, Loc. cit.

⁸ Saemisch, Handbuch der ges. Augenheilk., 11, pt. ii, 128; Pagenstecher, Arch. f. vergl. Ophthal., 1912, 2, 424; Takamura, Archiv. f. Augenheilk., 1911, 70, 335.

⁹ Lewin and Guillery, Wirk. v. Arzneim. u. Gift. a. d. Auge, 1905, 1, 696.

¹⁰ Prochownik, Loc. cit.

of dry naphthalin dissolves without color in 2.5 grams of melted chloral hydrate, and remains colorless after ten minutes' warming on the water-bath (α -naphthol becomes red, β -naphthol blue). If the above mixture be warmed with 5 drops of hydrochloric acid, a pale rose color may develop (α -naphthol becomes dark greenish blue, β -naphthol yellow); if zinc be added to the above mixture, a violet or brown color develops (α -naphthol becomes blue violet, β -naphthol dark brown, and both become fluorescent with alcohol).

OILS OF TURPENTINE, SAVIN, AND CEDAR

A number of plants belonging to the Coniferae contain volatile oils that are of some interest in toxicology; the most important of these are the oils of turpentine, savin, and cedar.

Oil of Turpentine.—Oil of turpentine (*Oleum terebinthinæ*, U. S. P.) is a volatile oil distilled from turpentine, the latter being an oleoresin obtained from *Pinus palustris* and other species of *Pinus*. When pure, oil of turpentine is composed of one or more terpenes, but, as usually seen, it contains oxidation products of these hydrocarbons. It is a colorless or light yellowish, highly inflammable oil, moderately soluble in alcohol, and very slightly so in water. It has a hot, burning taste, and when applied to the skin, causes irritation and redness. It is extensively used in the arts as a solvent.

Poisoning with oil of turpentine has resulted from its use in medicine, as, *e. g.*, an anthelmintic, or has been due to accident or occasionally to the use of the substance for the purpose of suicide, or, more frequently, for securing abortion¹; in rare instances it has been used for homicidal purposes. The vapors are also poisonous.

When a large dose is taken internally, there is a sensation of warmth in the throat and stomach, followed by abdominal pain, vomiting, and diarrhea. The pulse is weak, and the respiration becomes slow and irregular; then follow, in some cases, nervous symptoms²—excitement and muscular incoördination, suggesting alcoholic intoxication,³ and convulsions—and death in coma. There is usually great irritation of the urinary tract,⁴ as shown by strangury, hematuria, albuminuria, and often painful erections. The urine has the odor of violets. Sometimes there is complete suppression of the urine. Various forms of skin eruptions have been described; in one case a scarlatinoid rash followed the taking of 55 minims of turpentine.⁵

Severe poisoning may result from the inhalation, especially in a confined space, of the vapors of turpentine, as by painters or varnishers.⁶ The symptoms are conjunctivitis, bronchitis, headache, dizziness, stag-

¹ Kendall, *Med. Rec.*, 1892, 42, 572.

² Carles, *Jour. de méd. de Bordeaux*, 1911, 41, 376.

³ Lodemann, *Med. Klinik*, 1920, 16, 340.

⁴ Grapnel, *Brit. Med. Jour.*, 1901, i, 340.

⁵ Blackwood, *Jour. Amer. Med. Assoc.*, 1913, 61, 412.

⁶ Compare Lehmann, *Arch. f. Hyg.*, 1899, 34, 321; Harris, *Arch. Int. Med.*, 1918, 22, 129.

gering, drowsiness, and even unconsciousness, and often strangury, and irritation of the kidneys, with bloody urine.¹

The **lethal dose** of the oil of turpentine is not known. An infant fourteen weeks old died in fifteen hours after taking $\frac{1}{2}$ ounce (15 c.c.) of the drug.² In another case an infant, aged five months, died soon after taking a teaspoonful. On the other hand, an infant of fourteen months recovered after taking 4 ounces (120 c.c.). A woman died in a few hours from about 6 ounces (180 c.c.).³

The **treatment** consists in the evacuation of the stomach and the administration of demulcents and stimulants. Little is known about the *postmortem appearances*.

Properties and Tests.—The rectified oil of turpentine consists mainly of terebenthene. It is a mobile, colorless liquid with an odor of turpentine and is highly refractive. That of French origin rotates polarized light to the left, that of English origin to the right. Turpentine oil has a specific gravity of 0.864, and a boiling-point of 156° to 160° C. (312.8° to 320° F.); it burns with a smoky flame. It is insoluble in water, dilute acids, and dilute alkalis; it is soluble in absolute alcohol, ether, petroleum ether, chloroform, and benzene. These solvents are used for extracting it from tissue and stomach contents. If the oil is treated with concentrated hydrochloric acid and allowed to stand, crystalline rhombic plates of terebenthene dihydrochlorid are produced. These crystals are insoluble in water. If a few drops of the oil are stirred in a small porcelain dish with a drop of hydrochloric acid and a drop of ferric chlorid, and warmed, there develops a rose color, which changes to violet red, then to blue.

Oil of Savin.—Savin is the tops of *Juniperus sabina*, an evergreen growing in Europe and said to occur also in the northern part of the United States. The active principle is contained in an oil, which is closely related to the oil of turpentine; like the latter it is a powerful local irritant.

The tops of savin, in the form of a decoction, have been used by the laity from the most ancient times as an abortifacient; more recently the oil has been used for the same purpose. Most cases of death from savin have resulted from such a practice.

The **symptoms** of savin-poisoning are very similar to those resulting from oil of turpentine, but savin is a more active poison than the latter; there are violent abdominal pains, bloody vomiting and purging, diminution of the urine, which may be bloody, strangury, or anuria, irregular respiration, unconsciousness, convulsions, and death in collapse. Abortion frequently occurs in pregnant women, but it is doubtful whether savin has any specific action upon the uterus, although it is used in treating amenorrhea; the abortion may be the indirect result of the hyperemia of the pelvic organs caused by the irritation of the intestines. In a number of cases death has occurred without

¹ Reinhard, Deutsch. med. Woch., 1887, 13, 256; cf. Schulz, Münch. med. Woch., 1900, 47, 957; Rand, Amer. Jour. Public Health, 1916, 6, 830.

² Miall, Lancet, 1869, i, 360.

³ Maund, Amer. Jour. Med. Sci., 1858, 36, 561.

expulsion of the fetus. Lewin¹ collated 20 cases in which abortion occurred with 9 deaths; also 11 cases of poisoning in which abortion did not occur, but in 4 of which death resulted.

Fatal Dose and Fatal Period.—As the victims usually gather the tops of the plants themselves and make an infusion, of which they drink more or less, it has not been possible to determine how much savin is required to produce death; moreover, in most cases much of the oil is volatilized by the boiling.

Death may occur in twelve hours or it may be delayed for four or five days. In a case described by Blyth,² a woman died in about



FIG. 66.—Savin (*Juniperus sabina*).

twenty-six hours from an unknown quantity of infusion of savin tops. Postmortem, the pharynx was found reddened and the gullet congested; the stomach was congested and contained savin tops. The odor of savin is usually noticed in the stomach and sometimes in other organs.

The **treatment** consists in the evacuation of the stomach and the administration of demulcent drinks; stimulants may be necessary in the stage of collapse.

¹ Lewin, *Die Fruchtabtreibung durch Gifte*, Berlin, 1905.

² Blyth, *Poisons*, 4th ed., 1906, 475.

Oil of Cedar.—The tops of *Juniperus virginiana*, the red cedar, a tree growing in all parts of the United States, contain a volatile oil that is very similar to that of savin. Most cases of poisoning (13 of 19 of those recorded between 1845 and 1916¹) have resulted from its use as an abortifacient; abortion was rarely if ever produced, but death resulted in at least 5 cases. Occasionally poisoning has resulted from accident² or from an attempt at suicide.³

The symptoms⁴ have been burning in the stomach, vomiting (sometimes bloody), violent convulsions (epileptiform in character and in one case⁵ recurring about every ten minutes), bloody froth at the mouth, irregular respiration, weak, slow, and sometimes intermittent pulse, stupor, unconsciousness, and coma. In cases of recovery there have been diuresis (Clegg) or anuria (for thirty-six hours, Brown).

The symptoms appear very soon after the poison is taken, often within a few minutes; death (after taking about an ounce) has occurred within an hour (Wait, McNally) or has been delayed twenty-six hours.⁶ The smallest fatal dose recorded was 1 ounce (30 c.c.); recovery has followed this dose (with treatment). About 90 minims (5.5 c.c.) (Clegg), and $\frac{1}{2}$ ounce (15 c.c.) (Brown) have caused extremely severe symptoms.

The treatment consists in washing out the stomach, or the injection of apomorphin; otherwise it is symptomatic.

At autopsy the gastric contents have a pronounced odor of oil of cedar; gastro-intestinal irritation with engorgement of the subserous vessels, also pulmonary edema (McNally) have been described.

Isolation.—The well-diluted material is subjected to distillation with steam in the usual manner. The distillate, if ethereal oils are present, has the appearance of an emulsion and has a characteristic odor, depending upon the nature of the oil present. The distillate is saturated with sodium chlorid and shaken out in a separatory funnel with ether or odorless, low boiling-point, petroleum ether. The ether layer is separated and the ether allowed to evaporate spontaneously. If ethereal oils are present the residue will contain oily drops of characteristic odor which oftentimes is the only property available for identification.

Detection.—The best procedure is to compare the extracted oil with known samples of the various essential oils as to the following properties:

1. Odor.
2. Effects of light and air upon them.
3. Refractive indices.

¹ McNally, Med. Rec., 1916, 89, 330.

² Bailey, Phila. Med. and Surg. Rep., 1872, 26, 76; Ellyson, Therap. Gazette, 1890, 6, 371.

³ Wait, Boston Med. and Surg. Jour., 1849, 40, 469.

⁴ Compare Wait, Loc. cit.; Brown, Med. News, 1893, 63, 15; Holley, Detroit Rec. of Med., 1876, 11, 478; McNally, Loc. cit.; De Neen, Amer. Jour. Surg., 1919, 33, 277.

⁵ Clegg, Phila. Med. Jour., 1901, 8, 964.

⁶ Bolles, Med. and Surg. Rep. of Boston City Hospital, 1877, 2 S., ii, 270.

4. As effected by the following reagents¹:

- (a) Ether solution of bromin (1 : 20).
- (b) Alcoholic solution of hydrogen chlorid.
- (c) Concentrated pure sulphuric acid.
- (d) Molybdic, sulphuric acid (Fröhde reagent).
- (e) Ferric chlorid, sulphuric acid solution (1 part aqueous (1: 20) FeCl₃, and 6 parts concentrated H₂SO₄).
- (f) Fuming nitric acid.

CAMPHOR

Camphor (Camphora, U. S. P., C₉H₁₆CO), a ketone obtained from *Cinnamomum camphora*, forms white, translucent, crystalline masses that are almost insoluble in water, but that dissolve readily in alcohol, ether, benzene, oils, and chloroform. It melts at 176° to 178° C. (348.8° to 352.4° F.). The preparations of camphor ordinarily used are the Spiritus camphoræ (U. S. P.) and the Linimentum camphoræ (U. S. P.), or camphorated oil.

Camphor is irritant to the skin and mucous membranes; after its absorption it acts first as a powerful stimulant and then as a depressant to the central nervous system.

Many cases of accidental poisoning,² especially among children, are reported; thus the liniment has been mistaken for castor oil³ with serious results. There is a belief among the laity that camphor will prevent conception, and a few cases of poisoning from such use are reported.⁴ Camphor is used extensively as a household remedy for colds, a practice that occasionally leads to mild cases of poisoning.⁵

Symptoms.—The first symptoms⁶ are usually a burning sensation in the throat and stomach, vomiting, thirst, blurred vision, roaring in the ears, dizziness, headache, and rapid pulse. These symptoms are followed in from ten minutes⁷ to several hours⁸ by hallucinations, delirium, and convulsions; the latter may develop very suddenly. There may be several convulsive attacks, especially in children; these may be mild or very severe, and similar to those of epilepsy.⁹ Unconsciousness follows; if the patient recovers, he often remains in a dazed condition for some time. Other symptoms are abnormal sensations of various kinds, dilatation of the pupils, symptoms of enteritis and of irritation of the kidney, as shown by strangury, albuminuria, or anuria, cold perspiration, cyanosis, and a fall, or sometimes a rise, of tempera-

¹ G. Dragendorff, 42, also A. Ihl, Chem. Ztg., 1889, 13, 264; also L. Rosenthaler, Zeitsch. f. anal. Chemie, 1905, 44, 292.

² See, e. g., Moore, Brit. Med. Jour., 1898, ii, 717; May, Ibid., 986.

³ Brothers, Medical Record, 1887, xxxii, 734; Macleod, Brit. Med. Jour., 1896, i, 1556; Benz, Jour. Amer. Med. Assoc., 1919, 72, 1217.

⁴ Berkholz, St. Petersburg. med. Wchnschr., 1896, 21, 491; Pollak, Wien, med. Presse, 1874, 15, 258.

⁵ Spurgin, Brit. Med. Jour., 1898, ii, 84.

⁶ Compare Neumann, Therap. Monatsch., 1910, 24, 325; Koppang, Jour. Amer. Med. Assoc., 1913, 60, 330.

⁷ Macleod, Loc. cit.

⁸ Brothers, Loc. cit.; Chodounsky, Wien. med. Presse, 1889, xxx, 262.

⁹ Austregesillo, Jour. Amer. Med. Assoc. (abs.), 1915, lxiv, 1694.

ture. The pulse is irregular; the breath and urine smell of camphor. Nausea, faintness, and loss of appetite may continue for several days.

Fatal Dose and Period.—Most of the fatal cases have occurred among children. A child aged two died four hours after swallowing a quantity of camphor estimated to be about 15 grains (1 gm.).¹ Another child of the same age recovered after taking a similar dose.² A child aged two years and eight months died eighteen hours after taking what was thought to be about 30 grains (1.95 gm.).³ A child of sixteen months died in a few hours after taking 15 grams of a 20 per cent. camphorated oil.⁴ The fatal dose for an adult is not known. A woman took 184 grains (12 gm.) in order to bring on an abortion. The usual symptoms of camphor poisoning, and abortion, followed by death on the sixth day, occurred.⁵ It is not certain whether death was due to the effects of the abortion or to those of the camphor. Six or 7 grains (0.46 gm.) have caused toxic symptoms in an adult; on the other hand, patients have recovered from 150⁶ (9.75 gm.) and from about 200⁷ grains (13 gm.). In a case reported by Rubsamen⁸ 170 c.c. of 10 per cent. camphorated oil placed in the peritoneal cavity caused the usual symptoms and death on the third day.

Treatment.—Evacuation of the stomach and bowels is indicated; for the latter purpose saline purgatives or calomel should be used. Castor oil and alcohol are contraindicated, as they favor the absorption of the poison. Bromids and morphin may be used to relieve the convulsions.

There are no characteristic *postmortem appearances*, but the organs have the odor of camphor.

Numerous cases of poisoning,⁹ especially in children, have been reported from the application of *menthol*, a compound closely related to camphor and obtained from peppermint, and also from compounds of menthol, to the nasal mucous membrane in coryza; the symptoms were chiefly those of a reflex spasm of the glottis.

Isolation.—General method of distillation. The distillate is then shaken out with benzene which takes up the camphor. After evaporating the benzene on a warm water-bath, the camphor remains as a residue. This residue is purified by several recrystallizations from 50 per cent. alcohol.

Tests.—1. Melting-point is 176° C. (348.8° F.).

2. Characteristic odor, and spontaneous volatility.

3. Ten per cent. solution of camphor in alcohol, rotates polarized light 42.8° to right.

¹ Finley, Medical Record, 1887, xxxi, 125.

² Tidcombe, Lancet, 1897, ii, 660; cf. Miller, Jour. Amer. Med. Assoc., 1914, lxiii, 579.

³ Davies, Brit. Med. Jour., 1887, i, 726.

⁴ Barker, Brit. Med. Jour., 1910, i, 921.

⁵ Jour. de chim. méd., 1860, 21.

⁶ Brothers, Loc. cit.

⁷ Menzies, Edinb. Med. Jour., 1873, xviii, 1004.

⁸ Rubsamen, Zentralbl. f. Gyn., 1912, 36, 1009.

⁹ Lublinski, Berl. klin. Woch., 1912, 49, 261.

Estimation.—The purified material, obtained by recrystallization, is dried and weighed as such. Further this residue can be dissolved in alcohol and its rotation determined. On the basis of the above mentioned rotation of a known amount, the quantity present in the unknown can be calculated.

PHENOL (CARBOLIC ACID)

Few of the powerful poisons are so easily accessible to the public as is phenol, owing to its extensive use as a disinfectant. Phenol is a distinctly modern poison, the first case of poisoning having occurred in 1864, but in recent years it has either been at the top or near the top of the list of poisons causing death in the United States and England. Thus, in the registration area of the United States in 1909, 1621 of the 3376 cases of death due to poison (in which the kind was specified) were due to phenol. In England and Wales, 1912–13, phenol was responsible for 179 of the 1433 deaths from poison; only opium and its derivatives and hydrochloric acid were responsible for a greater number of deaths. There were 1740 deaths in England and Wales, 1901–18, due to phenol. Of 796 deaths from poisoning in St. Louis, 1910–14, 506 were due to phenol. The most frequent source of poisoning has been its use for suicidal purposes; it was the agent employed in 1466 of the 2372 cases in the United States in 1909 in which the poison was specified; in St. Louis, 1910–14, it was responsible for 490 of the 692 cases of suicide by poisons; of 1018 suicides by poison in England and Wales, 1912–13, phenol was employed in 152 cases. The next most frequent source of poisoning has been accidental: in the registration area of the United States in 1909 phenol was responsible for 155 of the 1004 cases of accidental death due to poisoning in which the kind of poison was specified. In many cases the accidents were due to the mistaking of phenol for other drugs or for alcoholic drinks. It is rarely used for criminal purposes.¹ Severe and fatal cases have resulted from its application to the skin (as when a chemist stepped into a pool of phenol waste and did not remove the clothing).² For several years following its introduction—in 1863 by Lister—as an antiseptic in surgical practice phenol caused many cases of poisoning from its absorption from wounds or from the skin³; surgeons likewise suffered severely from its effects. Death has also resulted from the carbolate of sodium.

Properties.—Pure phenol (Phenol, U. S. P.; carbolic or phenic acid, C_6H_5OH) is hydroxybenzene obtained from coal-tar or made synthetically. It “occurs in colorless, interlaced, or separate needle-shaped crystals, or as a white, crystalline mass, sometimes acquiring a red tint; having a characteristic, somewhat aromatic odor,” and a burning taste. The crystals melt at from 40° to 43° C. (104° to 109.4° F.); the boiling-point is 181.5° C. (358.7° F.). It is soluble in about 15 parts of water, but becomes liquid when 10 parts of water are

¹ See, however, Coester, *Vierteljahresschr. f. ger. Med.*, 1896, 11, 303.

² Hamilton, *Jour. Amer. Med. Assoc.*, 1917, 68, 1445.

³ Lucas, *Lancet*, 1897, ii, 537.

added to 90 parts of the crystals; the liquefied phenol of the U. S. P. contains not less than 87 per cent. of pure phenol. Phenol is readily soluble in alcohol, ether, chloroform, and glycerin. The aqueous solution is neutral, or at most only faintly acid, to litmus.

Phenol is a general protoplasmic poison, hence it is a valuable antiseptic. It precipitates proteins, but the combination is loose and the poison readily penetrates the tissues and causes necrosis. It exerts a numbing or even an anesthetic action upon sensory nerves. Aside from its local action, phenol produces marked changes in the central nervous system. There may be some stimulation at first, but this soon gives place to great depression. Phenol is rapidly absorbed not only from the stomach and intestines but also from the rectum, from serous cavities, from wounds, from the intact as well as from the diseased skin, and, in the form of vapor, by the lungs.

A part of the phenol absorbed is oxidized in the body to hydroquinol and pyrocatechol; a part is excreted in the urine unchanged, a part in combination with sulphuric and glycuronic acids. The hydroquinol and pyrocatechol formed are also excreted in combination with these acids. These combinations are unstable and tend to undergo further oxidation, by which colored substances are formed which tend to render the urine "smoky."

Symptoms.—The symptoms of phenol poisoning are due partly to the local, partly to the constitutional, effects. Applied to the skin, there is a sense of tingling and numbness that may amount to almost complete anesthesia. In concentrated form a white eschar is formed that falls off in a few days, leaving a bright brown stain. When applied for some time and prevented from evaporating, phenol may cause extensive dry gangrene of the part; this result has followed the use of so dilute a solution as 1 per cent.¹ Sometimes severe eczema results; a number of such cases, beginning with a burning and itching erythema, followed in some cases by local edema, have resulted from sweat bands made of imitation leather into the composition of which phenol entered.²

Taken internally phenol causes a burning pain in the mouth, throat, and stomach. Vomiting usually results, but it is not as constant or persistent as after other corrosive poisons. In concentrated form it acts as an energetic corrosive.

Constitutional effects begin very soon after the poison is absorbed by whatever channel this occurs. In mild cases of poisoning the chief symptoms are headache, dizziness, and sometimes excitement and mild delirium; the countenance is pale, the respiration is irregular, and the pulse is small. Vomiting is also a frequent symptom, especially if the poison has been taken by the mouth. The breath usually smells strongly of the poison. In severe cases of poisoning there are great muscular weakness and pallor of the face; the latter is covered with a clammy sweat. The patient soon becomes unconscious, the pulse is

¹ Harrington, *Amer. Jour. Med. Sci.*, 1900, 120, 1.

² Müller-Hess, *Deut. med. Woch.*, 1920, 46, 491; Hölker, *Ibid.*, 492; Schemel, *Münch. med. Woch.*, 1920, 67, 700.

weak and rapid, and the respiration irregular. The skin is livid and blue. Death results from failure of the respiration.

Occasionally there is a rise of temperature, which, however, is soon followed by a fall. In some cases general convulsions have occurred; in others there were convulsive twitchings of the face or of the legs. Convulsions occur more frequently in cases of poisoning in children.¹ The pupils are generally contracted and the cornea is insensitive. Occasionally consciousness may return and death occur later.

The urine is usually of a dark color, and this color increases when the urine is exposed to the air for some time. The preformed sulphates of the urine may disappear completely. There are usually albumin, blood, and other indications of severe irritation of the kidney, or the urine may be suppressed.

In the earlier days of the use of phenol as an antiseptic a form of chronic poisoning was sometimes observed among surgeons; the chief symptoms were disturbances of digestion, loss of appetite, sensations of nausea, headaches, diarrhea, and various forms of skin eruptions. Chronic nephritis frequently developed and was the usual cause of death.

Fatal Dose.—The fatal dose of phenol taken internally was placed by Falck at about $\frac{1}{2}$ ounce (15 gm.). In a series of cases collected by this author most of the patients taking this or a larger dose died, while most of those who took a smaller dose recovered. Death has, however, resulted from the taking of much smaller doses; thus a woman died from 22 grains (1.4 gm.),² while 1 dram (3.7 c.c.) of the liquid phenol proved fatal in twenty-three hours to a girl of seventeen.³ It is said that most cases in which 60 grains (3.9 gm.) of the acid were taken and retained, and the proper treatment was not given, ended fatally. Six or 7 grains (0.44 gm.) have caused severe symptoms. On the other hand, recovery has frequently followed the taking of 1 ounce (30 gm.). In one case abortion occurred after $1\frac{1}{2}$ ounces (45 gm.), but the girl recovered.⁴ In another case a patient recovered, under very prompt treatment, from "nearly an ounce and a half."⁵ The fatal dose depends largely upon the promptness with which treatment is given.

Very small quantities of phenol when introduced into wounds or into the body cavities will cause death. Thus in one case a uterine douche containing 1 dram (3.9 gm.) of phenol to a quart of water caused the death of a woman in one hour and forty minutes, although much of the liquid was returned; the symptoms were thirst, vomiting, rise of temperature to 108.5° F., and violent delirium.⁶ From 15 to 30 grains (1–3 gm.) may be regarded as a fatal dose under such circumstances.

¹ See case of Abrahams, *Pediatrics*, 1900, 9, 241. (Infant, seven days old, fatally poisoned by nurse touching groin with her thumb and index-finger that had come in contact with pure carbolic acid; the temperature rose to 105° F. Death in ten hours.)

² De Vries, *Therap. Monatsh.*, 1890, 4, 644.

³ Wilkinson, *Therap. Gaz.*, 3 s., 1892, 8, 220.

⁴ Taliaferro, *Weekly Med. Rev.*, 1883, 8, 55.

⁵ Cassidy, *Dominion Med. Monthly*, 1896, 6, 488.

⁶ Edmunds, *Med. and Surg. Reporter*, 1887, 57, 345.

A little more than 3 grains (0.2 gm.) injected into the rectum of a child aged eight caused severe poisoning.¹

Fatal Period.—The course of phenol poisoning is rapid. In a large percentage of cases death occurs within one or two hours and it is not often delayed more than twelve hours. After very large doses death may occur within a few minutes. In one case a girl of seventeen died within ten minutes after taking about 1 ounce (30 c.c.).² In another case about a quart of the crude acid was swallowed, but death did not take place for seven hours. In exceptional cases death may be delayed for sixty hours or even for four or five days. Death may result after several—*e. g.*, six—days from pneumonia caused by the aspiration of vomited matter into the lungs during unconsciousness.³

Death may occur within a very few minutes after the external application of phenol, or it may be delayed for several days.

Treatment.—If the poison has been swallowed, the stomach should be washed out with warm water; this should be done even if some time has elapsed since the poison was taken, for phenol remains in the stomach for a considerable period.⁴ Evacuation of the stomach by emetics is much less satisfactory; in some cases they fail entirely. Lime suspended in syrup has been recommended in the hope that an insoluble compound may be formed in the stomach. Benefit seems to have followed the administration of milk or white of eggs; these act not only as demulcents, but the albumin combines with the phenol to form compounds, but these should be promptly removed. Intravenous saline infusions may be of value in the circulatory depression and the application of heat in cases of collapse.

The sulphates and alcohol have, at different times, been supposed to be antidotal to phenol. A strong solution of sodium sulphate introduced into the stomach may delay the absorption slightly but has no other action. Alcohol seems to be of value only as a solvent for rapidly removing the phenol from the skin and mucous membranes and so preventing its escharotic action. Administered by mouth after phenol has been swallowed it increases the danger; lavage of the stomach with dilute alcohol (10 per cent.) has been recommended by some, but condemned by others.⁵

Postmortem Appearances.—When the poison has been taken by the stomach, there may be brownish, shrunken patches on the skin about the mouth. The mucous membrane of the mouth, esophagus, and stomach may be white, corrugated, and partly detached, and the edges of the affected parts are often hyperemic; if the case is one of long duration, these patches are red. In many cases the mucous membrane of the stomach and intestines is reddened and inflamed. The urine is usually of a dark or dark-greenish color unless death occurred

¹ Villebrun, *abs. Med. Rec.*, 1885, 28, 601.

² Marwood, *Austral. Med. Gaz.*, 1893, 12, 78.

³ Schleicher, *Deut. med. Woch.*, 1891, 17, 9; Cahn, *Therap. Monat.*, 1911, 25, 431.

⁴ Sollmann, Hanzlik, and Pilcher, *Jour. Pharm. and Exp. Therap.*, 1910, 1, 409.

⁵ Macht, *Johns Hop. Hosp. Bull.*, 1915, 26, 98; Wilbert, *Publ. Health Rep.*, 1916, 31, 1046.

very quickly. The odor of the poison may be noticed in the body and in the urine. The blood is usually dark and fluid; the brain, the meninges, the lungs, the liver, and the spleen are often congested.

CASES OF PHENOL-POISONING

CASE 1.—Woman, aged sixty, took 2 ounces (60 c.c.) of pure carbolic acid. Was found, shortly afterward, unconscious; pulse thready and scarcely perceptible; extreme dyspnea; lips cyanotic; conjunctival and pupillary reflexes absent. Rectal temperature, 96° F. A stomach-tube was introduced into the pharynx and 4 ounces (120 c.c.) of alcohol were poured in. After two or three minutes the tube was introduced into the stomach and the organ washed out with warm water; the washing was repeated with diluted alcohol. Signs of improvement quickly appeared. Strychnin and other cardiac stimulants were administered. In one hour and a half the patient was cheerful and felt little discomfort. The urine, which had to be drawn off with a catheter, was brownish black, but contained no albumin. Recovery was complete in three days.¹

CASE 2.—Adult male took 1 ounce (30 c.c.) of pure carbolic acid. Patient seen in a few minutes. There was a strong odor of phenol on breath; the lips were stained white. One-tenth grain (0.0065 gm.) of apomorphin injected. No emesis having occurred, the dose was repeated in five minutes, but vomiting did not take place. Patient soon had difficulty in swallowing; the face, which was at first flushed, soon became pale and slightly cyanotic. Within a few, perhaps seven or eight, minutes after the poison was taken there were tonic spasms of the voluntary muscles with muttering delirium; patient seemed unconscious of his surroundings. A quart of milk was pumped into the stomach. Pallor increased and the body became cold to the touch. Respiration labored, pulse weak and intermittent, pupils contracted. Patient did not at any time complain of pain. He was placed in bed and various stimulants were given. Respiration ceased about fifty minutes after the poison was taken. Heart was found to be beating feebly. Artificial respiration was resorted to. In about a minute patient began to breathe again and continued to do so for thirty minutes, when both respiration and heart ceased. No autopsy.²

Isolation.—In most cases of poisoning by carbolic acid the odor is distinctly noticeable. The tendency of the poison to combine with sulphuric acid is such that the sulphates present in the system may be completely used up in the formation of phenol sulphuric acid, and the urine under such conditions will fail to yield a precipitate when treated with barium chlorid.

For the isolation of the poison, the material under examination is thoroughly macerated with 5 per cent. sulphuric acid and submitted to distillation with steam (see Fig. 3, p. 43) until the liquid that passes over fails to respond to Millon's test. As carbolic acid is not appreciably soluble in petroleic ether, the distillate may be shaken with this solvent for the removal of various impurities³ and the carbolic acid finally extracted with ether or benzene. As salicylic acid responds to many of the tests for carbolic acid, it may be well to exclude this substance by making the distillate alkaline in the cold with sodium carbonate and extracting repeatedly with ether. Under these conditions carbolic acid is taken up by the ether, while sodium salicylate remains in the aqueous fluid.

It should be noted that combined carbolic acid is a normal constituent of the body, and that its amount is materially increased under certain

¹ Rodman, Medical Record, 1900, lviii, 70.

² King, Medical Record, 1897, li, 158.

³ Jacobsen, Zeitschr. f. anal. Chem., xxv, 607.

pathologic conditions. It is, therefore, always necessary to supplement the extremely sensitive¹ tests given below by a quantitative determination. This is best accomplished by the method of Kossler and Penny, but as the limits of this book do not admit an adequate description of the method, the reader is referred to the original article² and to an excellent abstract by Huppert.³

Although the analyst may reasonably expect to find the greater part of carbolic acid in the combined form, it may, nevertheless, happen, and especially after the ingestion of large quantities, that the presence of the poison in the free condition may be demonstrated. It is, therefore, advisable to make a preliminary distillation of the material after faintly acidifying with acetic acid. Any carbolic acid that can be shown in the distillate under these conditions must have been present in the uncombined state⁴ and will have greater toxicologic significance than that obtained by the distillation of a fluid that is highly acid with sulphuric acid.

Tests.—1. Solutions of carbolic acid are colored red when boiled with Millon's reagent.⁵ The test serves to detect 1 part of carbolic acid in 2,000,000 parts of water, but the red color is produced also by all monophenols and by proteins.

2. Solutions of carbolic acid are colored intensely bluish violet by a trace of ferric chlorid. The presence of mineral acid, ammonia, or an excess of the reagent is prejudicial to the production of the blue color, and the reaction fails entirely in the presence of alcohol.

3. On warming carbolic acid in substance with caustic potash and chloroform a product is formed which dissolves in alcohol with a carmin-red color. The color is removed by acids and restored by alkalis.⁶ The test is given equally well by resorcin.⁷

4. To a dilute aqueous solution of carbolic acid that contains a trace of an alcoholic solution of ethyl nitrite is carefully added some concentrated sulphuric acid in such a manner that the liquids do not mix. A rose-colored ring will form at the surface of contact. The reaction will show the presence of 1 part of carbolic acid in 2,000,000 parts of water.⁸

5. From extremely dilute solutions of carbolic acid, bromin water precipitates white crystalline tribromphenol.⁹

¹ Almén, *Ztschr. f. anal. Chem.*, xvii, 170.

² Kossler and Penny, *Ibid.*, xvii, 117.

³ Neubauer and Vogel, *Analyse des Harns*, Wiesbaden, 1898, 785.

⁴ Reale, *Maly's Jahresbericht d. Thierchemie*, 1891, 404.

⁵ Millon, *Comptes rendus*, xxviii, 40. Dissolve mercury in an equal weight of 63 per cent. nitric acid, warming gently to start the reaction, and dilute the product with twice its volume of water. After standing overnight decant the clear reagent.

⁶ Guareschi, *Ber. d. d. chem. Ges.*, v, 1055.

⁷ Lustgarten, *Monatsh. f. Chem.*, iii, 719.

⁸ Eijkman, *Zeitschr. f. anal. Chem.*, xxii, 576. See also Rodillon (*Jour. pharm. chim.*, 1921, 7 S., 23, 136), who adds 1 drop of a 10 per cent. aqueous solution of NaNO_2 to 10 c.c. of the suspected solution and overlays sulphuric acid with this mixture when a double ring appears at the zone of contact, emerald green below and ruby red above.

⁹ Landolt, *Ber. d. d. chem. Ges.*, iv, 770; Benedickt, *Ibid.*, xii, 1005.

If the amount of phenol is small, this precipitate will only form slowly. The reaction is sensitive 1 to 60,000. This precipitate is composed of fine stars or needles, melting-point 95°C . (203°F .). It is insoluble in water and acid liquids, but soluble in alkalis, ether, and absolute alcohol. That bromin water precipitates several volatile and fixed alkaloids is no objection, for it may be applied to the distillation product, the bases having been previously fixed by sulphuric acid.

6. On warming a solution of carbollic acid with one-fourth of its volume of ammonia and a few drops of calcium hypochlorite solution, a transient blue color is produced that returns upon the addition of more hypochlorite or by shaking with air. Instead of hypochlorite solution, vapors of bromin may be employed.¹

7. To 50 c.c. of water add 3 drops of anilin and dilute from 5 to 10 drops of the mixture with 10 c.c. of water. Add as much sodium hypochlorite solution as will serve to change the blue color that is first formed into a brown, allow to stand a few minutes, and add the solution supposed to contain phenol and previously treated with a few drops of ammonia. In the presence of phenol a permanent blue color will be produced. This is Dragendorff's modification² of Jacquemin's well-known reaction.³

Jacobsen⁴ claims that the greater part of the poison will be found in the blood and the liver, and Jacquemin⁵ proposes the following short method of preparing an alcoholic extract to which his test may be applied. One hundred grams of blood or finely cut liver are digested for an hour with 2 per cent. sulphuric acid; the liquid is strained through a cloth, treated with an equal volume of 30 per cent. alcohol, and filtered; 30 c.c. of the clear fluid are used for the test given above.

The following color reaction may be of aid in differentiating between carbollic acid and the other phenols. Take up or extract the suspected material with chloroform. If to this chloroform extract a little solid potassium hydroxid is added and then slightly warmed the following colors may develop. If carbollic acid is present it turns red; naphthols, blue; thymol, dark red; pyrocatechin, yellowish brown; resorcin, red; hydroquinon, yellowish red to reddish brown; pyrogallol and phloroglucin, reddish yellow.

The following reagents have also been suggested for identifying individual phenols; ammonia plus tincture of iodine,⁶ formalin-sulphuric acid,⁷ potassium ferricyanid,⁸ and uranium acetate.⁹

Estimation.—1. The distillation with steam is carried out until all the phenol is present in the distillate. Bromin is now added to the distillate producing tribromphenol. This is filtered, washed, dried

¹ Cotton, *Bull. de la Soc. Chim.* (2), xxi, 8.

² *Ermittelung von Giften*, Göttingen, 1895, 121.

³ *Zeitschr. f. anal. Chem.*, xv, 367.

⁴ *Loc. cit.*

⁵ *Loc. cit.*

⁶ Manseau, *Bull. Soc. Pharm. de Bordeaux*, 1901, 41, 117.

⁷ H. Linke.

⁸ *Chemiker Ztg.*, 1900, 24, 299.

⁹ *Pharmaceut. Jour.*, 1902, 41, 267.

at 80° C. (176° F.), and weighed. One hundred parts of this compound represent 28.4 parts of phenol.

2. Determination of phenols plus cresols in urine. In normal individuals, 15 mg. of these phenols are produced in twenty-four hours. In a case of poisoning the amount is greatly increased. The method is as follows, according to Messinger and Vortman: 500 c.c. of urine are made alkaline with sodium hydroxid and evaporated to half the volume; water is now added to bring it to its original volume; 20 c.c. of concentrated sulphuric acid are added, and one-half of the volume is distilled off. The residue in the flask is again diluted to its original volume and again one-half of its volume distilled off. This operation is repeated three more times. The various distillates are combined, and rectified by distilling over calcium carbonate in order to remove volatile acids. This purified distillate is now put in a glass-stoppered flask, 20 c.c. of normal potassium hydroxid are added and warmed to 60° C. (140° F.). Tenth-normal iodine is now added until precipitation of the red di-iodophenyl iodide is complete as indicated by the supernatant liquid having a yellow color. Allow to cool, acidify with dilute sulphuric acid and dilute to certain convenient volume (250 c.c.). An aliquot portion (100 c.c.) is titrated with N/10 sodium thiosulphate. One c.c. N/10 iodine solution is equivalent to 1.566 mg. phenol or 1.797 paracresol.

DIHYDROXYBENZENES

The *dihydroxybenzenes* ($C_6H_4(OH)_2$) pyrocatechol (pyrocatechin), resorcinol, U. S. P. (resorcin), and hydroquinol (hydroquinone) are used to some extent in medicine and have caused a few cases of poisoning. The symptoms are very similar to those of phenol poisoning; the stimulating effect of these bodies upon the nervous system, however, is more marked than with phenol, for convulsions have occurred in some cases.

In one case 2 drams (7.76 gm.) of resorcinol, taken internally, caused cold sweats, stupor deepening very rapidly into collapse, with complete abolition of reflex movement. The temperature fell to 94° F.; the urine was of an olive-green color. Recovery was rapid.¹ A few cases of poisoning² (one of an infant, fatal³) have resulted from the absorption of resorcinol when applied to the skin; severe local effects followed its use in a "dandruff cure."⁴

GUAIACOL

Guaiacol (U. S. P., methyl-pyrocatechol), one of the chief constituents of wood-tar creosote has caused a few deaths.⁵ Most cases of poisoning have resulted from its extensive use, both internally and externally,

¹ Murrell, Med. Times and Gaz., 1881, ii, 486.

² Kaiser, Berl. klin. Woch., 1905, 42, 1039; Nothen, Med. Klin. 1908, 4, 1901; Graham and Tisdall, Can. Med. Assoc. Jour., 1922, 12, 730.

³ Nothen, Loc. cit.

⁴ Montgomery, Jour. Amer. Med. Assoc., 1913, 60, 2035

⁵ Wyss, Deut. med. Woch., 1894, 20, 296, 321.

in the treatment of tuberculosis. The symptoms are irritation of the alimentary tract, loss of consciousness, fall of temperature, and collapse. The urine shows the same changes as after phenol. In one case death occurred in a tuberculous patient eighteen hours after the external application of 30 grains (1.95 gm.).¹ A number of preparations containing guaiacol, or derivatives of guaiacol, have been used in medicine; their effects are similar to those of guaiacol.²

CREOSOTE

Creosote (Creosotum, U. S. P.) consists largely of guaiacol and creosol; it is obtained by the distillation of wood-tar. Its effects upon man are very similar to those caused by guaiacol. It is used as an application in toothache, and poisoning has resulted from such use³; its easy accessibility has led to several cases of accidental, as well as of criminal, poisoning.⁴ About 2 drams (7.4 c.c.) caused the death of an adult woman in thirty-six hours, while another patient recovered after drinking 6 drams (22.2 c.c.).⁵

Creosotal (creosote carbonate) has caused severe poisoning.⁶

Properties.—The term creosote is applied to a mixture of crude phenols obtained from the destructive distillation of wood-tar. The chief ingredients are guaiacol, pyrocatechin methyl ester [$C_6H_4(OCH_3)-(OH)$], creosol [$C_6H_3(CH_3)(OCH_3)(OH)$] (methyl homopyrocatechin), and phloral (methyl creosol). It is a yellow liquid with a penetrating smoky odor. It is difficult to distinguish between creosol and creosote by chemical tests, because they react similarly; an alcoholic solution of creosote turns blue with a small amount and green with a large amount of $FeCl_3$. The following is a fairly good test for differentiating: Creosote mixes freely with the B. P. collodium, while creosol and phenol at once coagulate it. If all three are present, they must be separated by fractional distillation.

For detecting carbolic acid in creosote Flückiger⁷ suggests mixing an aqueous solution of the sample with one-fourth its volume of ammonium hydroxid, wetting the inside of a porcelain dish with this solution, and carefully blowing bromin fumes on to the surface. A blue color appears if carbolic acid is present. If the sample contains only creosote, then the color is a dirty green or brown. Avoid excess of bromin, as this spoils the reaction.

¹ Lewin, *Lehrb. der Toxikol.*, 1897, 216.

² Moseigt-Moorhof, *Deut. med. Woch.*, 1894, 20, 168.

³ Editorial Note, *Brit. Med. Jour.*, 1870, i, 272.

⁴ Manouvriez, *Ann. d'hyg.*, 3 S., 1882, 7, 175; Purckhauer, *Friedreich's Blätter*, Nuremberg, 1883, 34, 430 (murder of infants by creosote). See Humphrey and Fleming (*Jour. Ind. and Eng. Chem.*, 1914, 6, 128); Fleming and Humphrey (*Ibid.*, 1915, 7, 652), and Humphrey, Fleming, and Bateman (*Ibid.*, 1921, 13, 618) for studies of the toxicity of wood preservatives containing creosote.

⁵ Schulze, *Münch. med. Wchnschr.*, 1894, 41, 219; see Freudenthal, *Medical Record*, 1892, 41, 456.

⁶ Stadelmann and Boruttau, *Münch. med. Wchnschr.*, 1907, 54, 1933.

⁷ *Arch. der Pharm.*, cxiii, 30.

PYROGALLOL

Pyrogallol (U. S. P.), (pyrogallie acid, trihydroxybenzene, $C_6H_3(OH)_3$) is used, in the form of an ointment, in the treatment of skin diseases, especially of psoriasis; it is also used in photography, in hair dyes, marking inks, etc. It is readily absorbed by the skin, especially from the diseased skin, and has caused a few cases of poisoning in this manner.¹ It has also been used for suicidal² purposes, and solutions intended for photographic purposes have been mistaken for alcoholic liquors, with fatal results.

The chief symptoms in poisoning by pyrogallol result from the effect of the poison upon the red blood-corpuscles; the latter become shrunken and lose their hemoglobin. The hemoglobin is converted into methemoglobin, and the blood, as a consequence, assumes a reddish-brown color. Icterus may follow, and the decomposition products of the red corpuscles cause nephritis with the appearance of albumin, epithelial cells, and blood in the urine; or the nephritis may lead to uremia. These blood changes lead to headache, cyanosis, chills, vomiting, diarrhea, and strangury; the pulse becomes small, and the urine assumes a dark brown color from the presence of oxidation products of the poison and of blood-pigment. In fatal cases the cyanosis becomes intense, tremors develop, and death occurs in a state of collapse.

The **fatal dose** is not known, but 75 grains (4.88 gm.) contained in about $3\frac{1}{2}$ ounces (108.8 gm.) of salve are said to have been fatal. Cases³ in which much more than 1 dram of pyrogallie acid was said to have been taken internally did not cause very severe symptoms and recovery soon followed. A man recovered after taking 120 grains (7.8 gm.) of the poison dissolved in alcohol, while another man who drank a quantity of the same liquid containing about 250 grains (16.25 gm.) died in five days from symptoms of nephritis.⁴ In other cases patients died in a state of coma in two or three days after taking about 15 grams.⁵

The **treatment** consists in removing the poison from the skin, or, if it has been taken internally, in washing out the stomach. Stimulants and bleeding, followed by saline infusions, or blood transfusion, are recommended. The inhalation of oxygen is said to have been beneficial.

Postmortem⁶ the skin has been found colored dark at the point of application. The kidneys were enlarged and were almost black; the pelvis of the kidney, the ureters, and the bladder contained a bloody liquid. Icterus has also been noticed.

Properties and Tests.—It forms colorless crystals having a bitter taste, melting at $131^\circ C.$ ($267.8^\circ F.$). It is soluble in 1.7 parts of water, less in alcohol and ether, difficultly soluble in chloroform, benzol, and carbon bisulphid. Its alkaline solution absorbs oxygen vigor-

¹ Neisser, Zeits. f. klin. Med., 1880, i, 88; Vollmar, Zeitz. f. Mediz. Beamte, 1896, 9, 68.

² Reilly, Brit. Med. Jour., 1897, ii, 81.

³ Banerji, Lancet, 1892, ii, 308.

⁴ Smith, Pacific Med. Jour., 1891, 34, 456.

⁵ Dalché, La Semaine méd., 1896, 16, 211; Reilly, Loc. cit.

⁶ Neisser, Loc. cit.; Reilly, Loc. cit.

ously, turning brown to black. It stains skin and hair brown. Ferrous salts added to its aqueous solution turns it dark blue; ferric salts, red. It reduces silver salts to metallic silver. If shaken with lime-water it turns violet to black.

CRESOL; "COAL-TAR DISINFECTANTS"

It is impracticable to consider the toxicology of cresol separately. Cases of poisoning with pure cresol are perhaps unknown, whereas such resulting from various proprietary "coal-tar disinfectants" into the composition of which cresol enters to a greater or less extent and the toxicity of which is largely determined by the amount of cresol present, are very common.

Cresol, U. S. P. ($C_6H_4(CH_3)OH$), is a mixture of the three isomeric cresols (methyl-phenols) obtained from coal-tar; the proprietary preparation "Tri-kresol" is stated¹ to contain 35 per cent. orthocresol, 40 per cent. metacresol, and 25 per cent. paracresol.

Of the three cresols the meta compound is less poisonous to mammals than is phenol, the ortho is more poisonous than phenol, and the para still more so.² Hale³ found tri-kresol to be about 0.9 as toxic as phenol.

The symptoms of poisoning are essentially the same as those of phenol.

Cresol is frequently used in the form of a suspension in water with soap; the *Liquor cresolis compositus* of the U. S. P. is such a preparation (50 per cent. cresol). This is very similar to the proprietary preparation "Lysol."

For many purposes so-called crude carbolic acid is used as a disinfectant; this is stated to have formerly contained a large percentage of phenol (up to 50 per cent.), but now to contain little phenol and to consist chiefly of higher homologues of phenol, especially cresol.

Other antiseptic and disinfectant preparations are made from tar oils; these contain varying amounts of cresol and other phenol homologues and hydrocarbons; creolin (Pearson) is said to contain 12.7 per cent. phenols (cresols, etc.), and 44.9 per cent. hydrocarbons held in suspension by rosin soaps.⁴ Some other coal-tar disinfectants have an analogous composition. Preparations containing a relatively high percentage of "higher phenol homologues" (phenols containing two or more methyl groups) are relatively less toxic for mammals, but more strongly germicidal than are those containing a higher percentage of phenol or cresol.⁵

Of these various proprietary coal-tar disinfectants, lysol is most frequently mentioned as a source of poisoning: 277 cases of lysol poisoning with 81 deaths (29.2 per cent.) were treated in two Berlin hospitals in the years 1904 and 1905; Friedländer⁶ believed that at

¹ New and Non-official Remedies, 1918, 91.

² Wandel, Arch. f. exp. Path. u. Pharm., 1907, 56, 161.

³ Hale, Bull. 88, Hygienic Lab. U. S. P. H. S., 1913.

⁴ Schmidt, Pharmazeutische Chemie, 1911, 2, 1095.

⁵ New and Non-official Remedies, 1921, 921.

⁶ Friedländer, Ther. Monat., 1908, 22, 536.

least 200 cases occurred yearly in Berlin. Poisoning by lysol constituted 35 per cent. of all cases of poisoning treated in 1904 to 1912 at one of the Hamburg hospitals¹; it was taken with suicidal intent by 425 persons in Hamburg between 1904 and 1917.² In 1906 to 1912 1603 fatal cases of lysol poisoning were officially reported in Prussia.³

Of 133 cases of lysol poisoning collated by Witthaus,⁴ 13 were by external application, with 3 deaths; 11 by uterine irrigation (in 3 cases to induce abortion), with 5 deaths; 107 by internal administration (2 by enema), of which 23 were accidental, with 7 deaths, 84 suicidal, with 21 deaths, and 2 homicidal, with 1 death. Death has resulted from 1 to 2 teaspoonfuls (3.75–7.5 c.c.) of lysol; recovery, however, has occurred after much larger doses.

Lysol causes both local⁵ and general symptoms⁶ similar to those caused by phenol; acute parenchymatous degeneration of liver and kidneys has been reported.

The fate of the cresols in the body is the same as that of phenol; part is excreted in combination with sulphuric and glycuronic acids; part is oxidized to hydroquinol and pyrocatechol, which are also excreted as sulphates and glycuronates.

Creolin is, according to Hale, about one-third as toxic for lower animals as lysol; several cases of poisoning (11 fatal cases in Prussia from 1906–12⁷) have been reported from it and also from analogous products.

Properties of Cresol.—At ordinary temperature the commercial cresol is a liquid containing all three (o, m, and p) cresols. It has a boiling-point between 198° and 203° C. (388.4° to 397.4° F.). It is insoluble in small quantities of 6 per cent. soda solution; with a large excess it forms crystalline scales, while carbolic acid is freely soluble in small or large quantities of alkaline solution. Cold petroleum dissolves cresol; on cooling with freezing mixture no crystals separate out. Carbolic acid, on the contrary, is but sparingly soluble in cold petroleum, and a solution of carbolic acid in hot petroleum, when exposed to sudden cold by a freezing mixture, separates out crystals from the upper layer of liquid. Bromin converts cresol into tribrom-cresol, but this is a liquid at ordinary temperatures, while tribrom-phenol is a solid. With ferric chlorid it gives a similar color reaction to phenol.

Properties of Lysol.—A clear, brown, oily fluid. It is composed of coal-tar cresols (fraction 182° to 210° C.—359.6° to 410° F.), and of soap solution (usually 1 : 1). It is soluble in equal volumes of alcohol, ether, chloroform, and benzene. On addition of water it gives a foamy solution. Dilute ferric chlorid added to an aqueous solution of lysol

¹ Weitz, Festschr. d. allg. Krankenhaus, St. Georg, 1912.

² Sieveking, Vierteljahresber. f. ger. med., 1918, 56, 163.

³ Das Gesundheitswesen im Preuss. Staat, 1905–1912.

⁴ Witthaus, Manual of Toxicology, 1911, 1187; cf. Seifert, Die Nebenwirkungen d. modern. Arzneimittel, 1915, 229.

⁵ Harrington, Jour. Amer. Med. Assoc., 1909, 52, 575.

⁶ Friedländer, Loc. cit. (Literature).

⁷ Das Gesundheitswesen im Preuss. Staat., 1905–1912.

produces a cloudiness and blue violet color, which quickly vanishes. To detect lysol one must prove the presence of both cresols and fatty acids.

THYMOL

Thymol, U. S. P., a phenol [$C_6H_3(CH_3)(OH)(C_3H_7)$] occurring in the oil of thyme and other volatile oils is used extensively as an anthelmintic, especially in hookworm infections, and is also an ingredient of various "antiseptic solutions"; it frequently causes mild and sometimes severe toxic effects. Its action is similar to that of phenol, but it is only about one-fourth as toxic as the latter; the local effects are, however, relatively slight, but it may cause a burning sensation in the stomach, and vomiting. In animals it causes weakness, apathy, and collapse; fatty degeneration of the liver and congestion or consolidation of the lungs are found postmortem. In poisoning in man there is nausea, vomiting, depression, headache, confusion, and roaring in the ears, giddiness, and collapse. In 44 per cent. of 464 administrations to man¹ the patients complained of slight ill effects (nausea, weakness, and giddiness).

Severe symptoms followed 40 grains of thymol, in 10-grain doses hourly in a child of four²; 60 grains (4 gm.) are said to have caused convulsions in a child of eight, and 6 grams are said to have caused the death of an anemic individual. On the other hand, the only symptom following 360 grains (24 gm.) taken at one time was diarrhea.³

Thymol is believed to have had in a few cases a deleterious action upon the thyroid.⁴

Properties.—Thymol is a p-methylisopropyl phenol, and occurs with cymene and thymene in oil of thyme and forms crystals which melt at 51° C. (123.8° F.), and having an odor similar to thyme. When fused the crystals boil at 230° C. (446° F.), and are volatile with steam. Thymol is insoluble in water.

Isolation.—By distillation with steam. The distillate is extracted with chloroform. This chloroform layer is carefully evaporated to dryness. Thymol is found in the residue.

Tests.—1. A little of this residue dissolved in a few drops of chloroform, and a little piece of caustic potash added yields a dark red color on warming, if thymol is present.

2. A little of thymol dissolved in a little glacial acetic acid and mixed with an equal volume of sulphuric acid, and slightly warmed, develops a violet-red color (Hammarsten, Rolbert).

NAPHTHOL

Two naphthols, the alpha- and beta-compounds, may be made from naphthalene; they bear the same relation to naphthalene that

¹ Stiles and Boatwright, Public Health Reports, July 18, 1913; cf. Darling, Barber, and Hacker, Jour. Amer. Med. Assoc., 1918, 70, 499. See, however, Barnes, Jour. Amer. Med. Assoc., 1922, 79, 964.

² Ashworth, Austral. Med. Jour., 1896, 18, 483.

³ Bozzolo, Jour. Amer. Med. Assoc., 1912, 58, 1744.

⁴ Edens, Med. Klinik., 1917, 13, 807.

phenol does to benzene. The beta-compound has been used in medicine as an external application in various skin diseases, especially in scabies, and internally as an intestinal disinfectant and anthelmintic; it has occasionally been used as a food preservative.

Properties.—Beta-naphthol (U. S. P.) $C_{10}H_7OH$, is a white or yellowish-white, crystalline powder with a faint phenol odor and a hot taste. It is soluble in 1000 parts of cold water, readily soluble in alcohol, ether, chloroform, glycerin, and solutions of caustic alkalis. Its melting-point is 120° to 122° C. (248° to 251.6° F.).

The physiologic action of beta-naphthol is similar to that of phenol, but it is a more powerful antiseptic; it has a destructive action on the blood and an injurious action on the kidney. It is readily absorbed from the skin, especially from the diseased skin, and most cases of poisoning have resulted from its use in scabies; α -naphthol is said to be more poisonous.

Symptoms.—In cases of poisoning the symptoms have been vomiting, unconsciousness, and irritation of the kidneys. Blood has appeared in the urine after the application of an alcoholic solution to the skin. In 2 cases of poisoning in boys, following the application of a 2 per cent. ointment to the skin in the treatment of scabies, there was severe nephritis, and one of the boys died in a little more than three weeks.¹ In another case² after the application of nearly 4 drams (15 gm.) of naphthol to the skin of a man for scabies, general eczema and, in fourteen days, an acute nephritis developed. A pregnant woman died in a little more than twenty-four hours after the application, in the form of an ointment, of about 1 dram ($3\frac{2}{3}$ gm.) to the skin for scabies; the symptoms were vomiting, somnolence, and unconsciousness, and later, numerous small hemorrhages from the skin.³

The extensive use of beta-naphthol as an anthelmintic, especially in hookworm infection, has led to a few cases of poisoning; in some of these irritation of the kidney seemed to be the most prominent symptom⁴; in others there was (after 18 gm.) a destruction of blood-cells with severe anemia, jaundice, enlargement of the spleen and liver.⁵

The urine is dark from the presence of naphthol, which is excreted in combination with glycuronic and sulphuric acids; in the later stages there is frequently albuminuria.

Retinal changes, and in one case cataract formation, following the medicinal use of naphthol have been described⁶; these changes are similar to those caused experimentally in animals by naphthalene.

The fatal cases have not been sufficiently numerous to allow of any definite statements as to the *fatal dose* and *fatal period*. Stern's case shows that 3 or 4 grams (1 dram) applied externally may cause

¹ Baatz, Centralbl. f. innere Med., 1894, 15, 857. See also Busquet, Jour. Amer. Med. Assoc., 1921, 79, 51.

² Lewin, Nebenwirkungen der Arzneimittell, 1897, 675.

³ Stern, Therap. Monatsh., 1900, 14, 165.

⁴ Orme, Brit. Med. Jour., 1915, ii, 176.

⁵ Smillie, Jour. Amer. Med. Assoc., 1920, 74, 1503.

⁶ Van der Hoeve, Arch. f. Oph., 1901-02, 53, 74; Ibid., 1913, 85, 305; Lewin and Guillery, Wirk. v. Arzneimitt. u. Gift. a. d. Auge, 1905, 1, 698.

death. Death has occurred in from twenty-four hours to three weeks; 18 grams taken by mouth has caused in some individuals very severe symptoms.

The **treatment** should be similar to that of phenol poisoning. If the drug has been applied externally, the parts should be thoroughly washed.

Postmortem Appearances.—Parenchymatous nephritis and extensive changes in the skin have been found.

Isolation and Tests.—Beta-naphthol may be extracted from the stomach contents or from the vomited matter with alcohol. On evaporation of the alcohol the residue gives a blue color changing to green and then brown when warmed with potassium hydroxid and chloroform (Lustgarten's test). It has been recovered from the urine by distillation with hydrochloric acid and by extracting the distillate with ether (for other tests, see Naphthalin).

SALICYLIC ACID

Salicylic acid (Acidum salicylicum, U. S. P.) (orthohydroxybenzoic acid, $C_6H_4.OH.CO_2H$) occurs in the form of small, white, needle-like crystals or as a light crystalline powder melting between 156° and 159° C. (312.8° and 318.2° F.); it is slightly soluble in cold water, and very soluble in alcohol and ether. It has a sweetish, afterward an acrid, burning taste.

Most of the cases of poisoning with salicylic acid have been medicinal and have resulted from the extensive use of the substance and its salts in the treatment of rheumatism; death has resulted from its absorption from alcoholic solutions, ointments, etc., applied to the diseased skin.¹ It was formerly often added to articles of food and drink as a preservative.

The symptoms in a mild case of poisoning, such as is frequently seen in the treatment of acute rheumatism, are nausea and vomiting, a feeling of fulness in the head, with ringing in the ears, dimness of vision, profuse perspiration, confusion, and dulness. With large doses of the free acid there is intense irritation of the throat and stomach, leading to vomiting and difficulty in swallowing; later there may be diarrhea. Flushing of the face, distressing dyspnea, weak pulse, sub-normal temperature, and, in more severe cases, convulsions, coma, and perhaps death in a state of collapse occur. Delirium and hallucinations have been described. In alcoholic patients these symptoms may not be unlike those of delirium tremens. There may be hemorrhages from the nose or uterus; abortion may occur.² Mild nephritis is a frequent symptom. Eczema and other skin eruptions may appear, and dimness of vision and deafness may continue for some time.

Long-continued use of salicylic acid and its salts is said to have led to a form of chronic poisoning in which the chief symptoms were

¹ Lenartowicz, Derm. Wehnschr., 1914, 59, 791; Keiss, Ther. Halbmonatsh., 1921, 35, 433.

² Binz, Berl. klin. Woch., 1893, 30, 985.

loss of appetite, diarrhea alternating with constipation, irritation of the kidneys, skin eruptions, and mental depression.¹ Such results are said to have followed the use of articles of diet preserved by salicylic acid.

Fatal Dose.—Individuals differ greatly in their susceptibility to salicylic acid. Moreover, in most of the cases in which death occurred there was disease, and it is impossible to determine to what extent the fatal issue was due to the drug.² In one case a patient suffering from acute rheumatism died after taking something over 1 ounce (31 gm.) in four days.³ Death has, however, been attributed to doses of 4, 5, and 10 grams. On the other hand, very large doses have been administered without poisonous symptoms appearing—for example, an ounce in twenty-four hours. An infant died from the application of a 10 per cent. ointment of salicylic acid to the head and neck.⁴

Treatment.—If the symptoms of irritation are not too marked, the stomach should be washed out with warm water. Milk and eggs or magnesium oxid may be administered, as in cases of poisoning with mineral acids.

Postmortem the lesions of gastritis, enteritis, and acute nephritis have been found; marked hyperemia of all the organs is usually present.

Isolation.—Extract the finely divided tissue, with acidified water in the water-bath. Filter, and make the filtrate alkaline with sodium carbonate and evaporate to dryness. The residue is acidified with sulphuric acid and then extracted repeatedly with ether. The ether is then evaporated, leaving a residue of the salicylic acid in crystalline form. See also method described in *Methods of Analysis* by A. O. A. C., 1919, page 118.

Tests.—1. The reactions with ferric chlorid, Millon's reagent, and bromin-water, which are described under Carboic Acid (p. 706), are equally applicable to the detection of salicylic acid. The following characteristic test, however, will easily distinguish between the two substances⁵:

2. A small amount of the suspected substance is heated in a test-tube with 1 c.c. of methyl-alcohol and half as much concentrated sulphuric acid. The mixture is allowed to cool and again heated, when, if salicylic acid be present, the odor of oil of wintergreen will be noticed.

3. Dissolve the residue from the ether extract obtained above in a little hot water. Cool 10 c.c. of the solution in a test-tube, add 4 or 5 drops of 10 per cent. potassium nitrite solution, 4 or 5 drops of 50 per cent. acetic acid, and 1 drop of 10 per cent. cupric sulphate solution, mix thoroughly, and heat to boiling. Boil for half a minute

¹ Vallin (reporter for Commission), *Bull. de l'Acad. de Méd.*, 22, Paris, 1886, 16, 583.

² See Goodhart, *Brit. Med. Jour.*, 1880, i, 130; Philpot, *Lancet*, 1877, ii, 626; Miller, *Jour. Amer. Med. Assoc.*, 1914, 63, 1107.

³ Quincke, *Berl. klin. Woch.*, 1882, 19, 710.

⁴ Zumbroich, *Monatsschr. f. Kinderh.*, 1918, 15, 167.

⁵ Curtman, *Zeitschr. f. Analyt. Chemie*, xxvi, 641.

and allow to stand for one to two minutes. In the presence of salicylic acid a blood red color will develop.

Estimation.¹—Dissolve the entire residue from the ether extract in a small amount of hot water and, after cooling, dilute to a definite volume (usually 50 to 100 c.c.), dependent on the amount of salicylic acid present. If the solution is not clear, filter through a dry filter. Dilute aliquots of the solution and treat with a few drops of 0.5 per cent. ferric chlorid solution or 2 per cent. ferric alum solution.

The ferric alum solution should be boiled until precipitate appears, allowed to settle, and filtered. The acidity of the solution is slightly increased in this manner, but it remains clear for a considerable time, and the turbidity caused by its dilution with water is much less and does not appear so soon as when the unboiled solution is used. This turbidity interferes with the exact matching of the color.

Compare the colors developed with that obtained when a standard salicylic acid solution (containing 1 mg. of salicylic acid in 50 c.c.) is similarly treated, using Nessler tubes or a colorimeter. In either case, and especially with ferric chlorid, avoid an excess of the reagent, although an excess of 0.5 c.c. of 2 per cent. ferric alum solution may be added to 50 c.c. of the comparison solution of salicylic acid without impairing the results.

Methyl salicylate, U. S. P. (oil of wintergreen), has occasionally caused death with symptoms of salicylic acid poisoning; a woman died in fifteen hours after taking about 1 ounce to secure abortion.² On the other hand, a child of two recovered after taking 1 ounce; olive oil was administered soon after the poison was taken.³

Phenyl salicylate (Salol, $C_6H_4.OH.COOC_6H_5$), a white powder melting at 42° C. (107.6° F.) and almost insoluble in water, but soluble in alcohol, ether, and chloroform, is partly decomposed in the intestine into phenol (40 per cent.) and salicylic acid (60 per cent.). The use of phenyl salicylate in medicine has led to a few cases of poisoning. The symptoms are partly those of phenol and partly those of salicylic acid poisoning; vomiting, fever, drowsiness, hematuria, roaring in the ears, etc., have been described. The urine is a dark olive green, as in phenol poisoning. In a case reported by Hesselbach⁴ a woman with a contracted kidney and suffering from acute rheumatism died on the fifth day after the administration of 2 drams (7.76 gm.) in the course of eight hours; another case is reported in which death was attributed to 15 grains (1 gm.) of salol taken twelve days previously.⁵

Detection.—Salol suffers hydrolysis in the body, giving rise to salicylic acid and phenol, both of which can be found in the urine. The best method of identification is to show the presence of both acids after submitting the suspected substance to saponification.

¹ A. O. A. C., 1919, 119.

² Pinkham, Boston Med. and Surg. Jour., 1887, 117, 548. See also Legrain and Badonnel, Jour. Amer. Med. Assoc., 1922, 78, 1140.

³ Myers, Jour. Amer. Med. Assoc., 1920, 75, 1783.

⁴ Hesselbach, Fortschr. der Med., 1890, 8, 453; see Sahli, Ibid., 661.

⁵ Chalpowski, Therap. Monatsh., 1891, 5, 213.

Acetylsalicylic acid ($\text{C}_6\text{H}_4\text{O}(\text{CH}_3\text{CO})\text{COOH}$; aspirin) is about one and a half times as toxic for man as is sodium salicylate¹ and sometimes causes severe symptoms in medicinal doses. Several cases² are reported in which 5 and 10 and even $2\frac{1}{2}$ grains caused pronounced edema of the face (so that it was "hardly recognizable"³), lips, eyelids, tongue, nose; difficult respiration, and cyanosis⁴ of the ears and fingers; restlessness, rapid, weak, or intermittent pulse; urticaria, vomiting, ringing in the ears. In one case (6 gm. in five days) amblyopia in one eye, disappearing in three days, was noted.⁵ Four grams taken in four hours caused considerable general cyanosis, cold extremities, weak intermittent heart, nausea, and vomiting.⁶

Habituation has been noted; a man⁷ increased the dose from 5 grains to 25 to 60 grains per day, but even after two years few toxic symptoms (constipation, slight digestive disturbances) were present. A case of chronic poisoning in a woman who for seven years took 20 grains of aspirin daily is reported⁸; the symptoms were conjunctivitis, wide-spread urticaria, diarrhea, vomiting, and edema of the tongue and fauces.

Properties and Tests.—A needle-like crystalline substance, readily soluble in water and in ether, alcohol, and chloroform. It can easily be extracted with water. The aqueous solution is then shaken out with ether. The ether extract is then evaporated. Aspirin is left in the residue. With sulphuric acid or with sodium hydroxid or boiling with water it is hydrolyzed to salicylic acid and acetic acid. These two substances are then tested for. Aspirin, as such, does not give a color with ferric chlorid; after hydrolysis it gives a violet color with this reagent.

PICRIC ACID

Picric acid (Trinitrophenol, U. S. P., $\text{C}_6\text{H}_2(\text{NO}_2)_3\text{OH}$) is a yellow crystalline substance, odorless, and having an intensely bitter taste, sparingly soluble in water, but readily soluble in alcohol, ether, chloroform, and benzene, and possessing a strong coloring power. It explodes when heated rapidly and when subjected to percussion. Picric acid and the picrates are much used in the arts, especially as a dye and as a constituent of certain high explosives (melenite, lyddite, emmensite). It is used to some extent in medicine, especially in the treatment of skin diseases and burns.

Poisoning has resulted from the use of picric acid as a means of

¹ Hanzlik, Jour. Amer. Med. Assoc., 1913, 60, 957.

² Morgan, Brit. Med. Jour., 1911, i, 307; Macht, Med. Rec., 1911, 80, 826; Hirschberg, Deut. med. Woch., 1902, 28, 416; Otto, Ibid., 1903, 29, 123; Meyer, Ibid., 1903, 29, 124; Gazert, Deut. Aech. f. klin. Med., 1900, 68, 142; Graham, Jour. Amer. Assoc., 1911, 56, 261. Shelby, Ibid., 1918, 71, 1381; Kitchin, Ibid., 1920, 74, 880.

³ Brown, Lancet, 1911, ii, 761.

⁴ Gilbert, Jour. Amer. Med. Assoc., 1911, 56, 1262; Reed, Ibid., 1914, 62, 773; Pridham, Brit. Med. Jour., 1919, 2, 632.

⁵ Jacobs, Ther. Monatsh., 1913, 27, 887.

⁶ Cooper, West Virginia Med. Jour., June, 1910, 4, 411.

⁷ Macht, Med. Rec., 1918, 94, 767.

⁸ Stiell, Practitioner, 1917, 99, 293.

committing suicide¹; in other cases workmen have been poisoned by handling it. Poisoning has also been caused by its absorption from the skin when applied in the form of a salve in skin diseases² or in the form of a solution or as a dusting-powder in the treatment of burns.³ It has been used by malingerers to simulate icterus and to escape military service.⁴

Picric acid is an irritant to the skin and mucous membranes. It precipitates albumin and so causes local necroses. It irritates the central nervous system and may lead to convulsions.

Symptoms.—When the poison is taken internally, the symptoms⁵ begin with pain in the abdomen, vomiting, and diarrhea. The urine is at first dark yellow, but later becomes of a red-brown color; it contains no bile. There may be anuria and strangury. The vomited matter and the feces are stained yellow. The conjunctiva and later the skin assume a yellow color; there may be yellow vision. Eczema and itching are common results. Prostration, stupor, fever, and occasionally convulsions followed by collapse, have been observed. The excretion of the poison is slow, and the yellow discoloration of the skin may persist for several days.

When poisoning has resulted, as in industrial cases, from the external application of picric acid, or the inhalation of the powder, and after its use in the treatment of skin diseases, intense itching and eczema have been prominent symptoms; stomatitis and gastro-intestinal symptoms have also resulted from some of the poison being carried to the mouth by the fingers. After the application of 7 grains (0.455 gm.) of picric acid to the vagina, the skin became yellow; the urine was red, and somnolence and burning in the stomach were noticed.⁶ Industrial poisoning⁷ has occurred chiefly in munition plants; the most frequent symptom is an irritating dermatitis from a direct action of the poison on the skin; the skin is stained yellow. There is bronchitis and strangury. Systemic symptoms, resulting apparently from the swallowing of the poison in the form of dust, are abdominal cramps, vomiting, diarrhea, loss of appetite, and loss of weight. Serious cases are unusual. A form of chronic poisoning has been noticed in laborers engaged in the manufacture of melenite: the symptoms were nasal catarrh, diarrhea, abdominal pains, and dizziness.

The **fatal dose** of picric acid is not known: from 15 to 30 grains (1–2 gm.) cause toxic symptoms, but recovery followed the taking of a “coffeespoonful”⁸ and also nearly 90 grains (6 gm.)⁹ or more.

Postmortem all the organs are found stained yellow.

¹ Karplus, *Zeitschr. f. klin. Med.*, 1893, 22, 210.

² Waldo, *Brit. Med. Jour.*, 1897, i, 331.

³ Editorial, *Lancet*, 1912, ii, 471.

⁴ Mende, *Deut. med. Woch.*, 1918, 44, 1440.

⁵ Adler, *Wien. med. Woch.*, 1880, 30, 819.

⁶ Chéron, *Jour. de Thérap.*, 1880, 7, 132.

⁷ Hamilton, *Jour. Amer. Med. Assoc.*, 1917, 68, 1445; Koelsch, *Zentralbl. f. Gervverbehg.*, 1919, 7, 185, 223.

⁸ Halla, *Prag. med. Woch.*, 1882, 7, 490, and 503.

⁹ Karplus, *Loc. cit.*

Treatment.—The treatment should consist in thoroughly washing out the stomach. The bowels should be emptied by the use of suppositories. Purgatives are not to be recommended, owing to the irritation of the intestine caused by them. The white of egg and milk may be administered, as they form insoluble compounds with the poison. The administration of large doses of dextrose has been recommended, as this substance was believed to aid the reduction of the picric acid to the less poisonous picraminic acid.¹

Isolation.—Extract the material under examination with alcohol, evaporate to a syrup and shake out the picric acid with successive portions of ether, making the material markedly acid with sulphuric acid before each addition of ether. Evaporate the united extracts, take up the residue in water, and use the solution for the following tests:

Tests.—1. Place a thread of wool and one of cotton in a small amount of the solution which has been faintly acidified and warmed. The wool is stained but the cotton is not. The color is withdrawn from the wool by suspending in dilute alkali.

2. On warming an alkaline solution of a picrate with a concentrated solution of potassium cyanid, potassium isopurpurate is formed, which imparts a blood-red color to the fluid. The red color is produced equally well by using glucose and an alkali.²

3. Ammoniacal copper sulphate forms with picric acid yellowish-green crystals which strongly refract light.

4. First reduce the picric acid solution with a hydrochloric acid solution of stannous chlorid; then add a little ferric chlorid, a blue color is produced. This is due to the production of amidoimidophenol—HCl during the reduction.

5. A little glucose in sodium hydroxid solution will, if heated, convert picric acid to picramic acid, giving a red coloration.

Dinitrophenol ("D. N. P."), a yellow or yellowish-white solid, used as a high explosive especially in France, and as an intermediate in one process for the manufacture of picric acid is more toxic than the latter; it is also more toxic than trinitrotoluene.

The symptoms³ in mild cases are lassitude, anorexia, nausea, vomiting; in more severe cases slight cyanosis, sweating, painful constriction of the chest, dyspneic respiration, diminution of the urine; in the most severe cases (especially in alcoholics) there is sudden onset of weakness, rapid rise of temperature to 104° F. or more, yellow sweat, intense thirst, tremors, excitement, sometimes convulsions, followed by unconsciousness, coma, and death. Postmortem there may be found edema of the lungs, but the other organs show nothing characteristic; occasionally⁴ an acute degenerative hepatitis similar to that caused by trinitrotoluene is found.

¹ Rymsza, Ein Beitrag z. Toxikol. der Pikrinsäure, Dorpat, 1889.

² Braun, Zeitschr. f. anal. Chem., iv, 185.

³ Medical Research Com., Spec. Rep., No. 11, 1918; Perkins, Publ. Health Rep., 1919, 34, 2335; Hamilton, Jour. Ind. Hyg., 1919, 1, 200.

⁴ Warthin, Internat. Assoc. Med. Mus. Bull., 1917, 7, 123.

NITROBENZENE

Nitrobenzene (nitrobenzol, "essence or oil of mirbane," "imitation oil of bitter almonds") is used extensively in the manufacture of anilin and of explosives, as a substitute for benzaldehyd (oil of bitter almonds) in perfumery and flavoring extracts, as an ingredient of shoe dyes, floor polishes, inks, etc. Many severe or fatal cases of poisoning have resulted from its being taken internally when used as a substitute for flavoring agents¹ or in alcoholic liquors,² or in confectionery or pastry; it has also been taken as an abortifacient and as a means of committing suicide.³ It has been absorbed, sometimes with fatal results, when spilled upon the clothes,⁴ or from the wearing of shoes recently dyed with liquids said to contain nitrobenzene⁵; infants have been poisoned by lying on cloth stamped with ink containing nitrobenzene⁶; poisoning has resulted from its application to the skin in the treatment of scabies or as a delousing agent⁷; from the application to a carious tooth instead of oil of cloves.⁸

Symptoms of poisoning have resulted from the use of soap ("almond glycerin soap") scented with nitrobenzene; this is most liable to occur when the soap is used in hot water.

Industrial poisoning results chiefly in plants making anilin.

Properties.—Nitrobenzene ($C_6H_5NO_2$) is an oily liquid, of a pale yellow color, having a specific gravity of 1.186 and a boiling-point of $205^\circ C.$ ($401^\circ F.$). It is insoluble in water and easily soluble in alcohol. The liquid burns readily with a luminous flame and has a sweet taste and an odor strongly resembling that of oil of bitter almonds.

The **physiologic action** of nitrobenzene is complex. It stimulates, then paralyzes, the central nervous system. It also produces marked changes in the blood; in fact, it is a good example of the "blood-poisons." The nature of the changes in the blood are not entirely understood. The blood becomes of a chocolate color, and some of the corpuscles are deformed, while others are destroyed. The spectroscope usually shows the absorption bands of methemoglobin, but often another absorption band which has been called the nitrobenzene hemo-

¹ Ames, Boston Med. and Surg. Jour., 1907, 156, 203; Tuszewski, Ther. d. Gegenwart, 1919, 21, 326.

² Bondi, Prog. med. Woch., 1894, 19, 129, 143; Spinner, Pharm. Zentrbl., 1913, 54, 871; Scott and Hanzlik, Jour. Amer. Med. Assoc., 1920, 74, 1000; Loeb, Bock, and Fitz, Amer. Jour. Med. Sci., 1921, 161, 539.

³ Schild, Berl. klin. Woch., 1895, 32, 187; Paterni, Policlinico, 1921, 28, Med. Sec., 353.

⁴ Hamilton, Jour. Ind. Hyg., 1919, i, 200; see Thomsen (Münch. med. Wchnschr., 1921, 68, 399) for poisoning from paint containing nitrobenzol.

⁵ Stifel, Jour. Amer. Med. Assoc., 1919, 72, 395; Miner, Ibid., 593; Sanders, Ibid., 1920, 74, 1518, and others. No statements as to the exact composition of the shoe dyes in question are given; anilin or derivatives of anilin may have been a factor.

⁶ Ewer, Deut. med. Woch., 1920, 46, 1078; Thomsen, Münch. med. Woch., 1921, 68, 399; Neuland, Med. Klin., 1921, 17, 903.

⁷ Wolpe, Deut. med. Woch., 1920, 46, 100.

⁸ Hogarth, Brit. Med. Jour., 1912, i, 183.

globin band, is present.¹ The blood becomes incapable of transporting oxygen and may contain but 1 per cent. of oxygen (normally it contains 17 per cent.; the oxygen capacity of the blood in human cases of poisoning has been found greatly reduced, in one case being only 6.2 volumes per cent.² This decrease in the oxygen-carrying power of the blood leads to a diminution of oxidation and to the appearance of abnormal products in the urine. Some of the nitrobenzene is reduced to paraminophenol, which appears in the urine.³

Symptoms.—When taken internally, there is a burning sensation, followed by numbness and tingling, but other symptoms may not begin for from one-quarter to two or three hours. The patient may walk about, eat, and appear quite normal,⁴ and then the symptoms begin quite suddenly. The face becomes grayish or bluish white, the lips and nails purple (these changes may precede the subjective symptoms); the pulse is weak and rapid; vision is disturbed; the gait is unsteady; the breath has the odor of bitter almonds; vomiting, dizziness, and headache follow, and finally coma comes on, often with great suddenness. Muscular twitchings and involuntary evacuation of the feces and urine may occur. Well-marked trismus, making the passage of the stomach-tube very difficult, has been observed a number of times. The temperature falls, and the respiration is frequently of the Cheyne-Stokes type. The pupils may be contracted or dilated, and do not react to light; there may be nystagmus. The urine is dark, smells of nitrobenzene, and contains a reducing substance. The blood is chocolate colored, thick, and viscid. Death usually occurs in coma from failure of the respiration; sometimes it results from the inspiration of vomited matter.

If the patient survives, the condition may apparently remain serious for several hours and then recovery occur rather rapidly. Nausea and vomiting may persist; there is frequently a rise of temperature, sometimes associated with necrotic processes, as in one case of the heels. Jaundice may appear in three or four days⁵ and continue until death occurs several (*e. g.*, seventeen) days afterward. Ehrlich and Lindenthal⁶ found the blood in such a case to be very similar to that of pernicious anemia.

If the poison is absorbed through the skin or lungs the symptoms may appear very quickly: the patient may become dizzy, faint, and collapse within a few minutes and death occur within an hour.⁷ In

¹ Filehne, *Arch. exp. Path. u. Pharm.*, 1878, 9, 329. These blood changes are constantly found in animals poisoned with nitrobenzene, and the methemoglobin band has been found in the blood in human cases of poisoning (Ehrlich and Lindenthal, *Zeits. f. klin. Med.*, 1896, 30, 427; Scott and Hanzlik, *Loc. cit.*), but the "nitrobenzene hemoglobin" band has apparently not been found in these; this compound seems, however, to be less stable than methemoglobin.

² Loeb, Bock, and Fitz, *Loc. cit.*

³ Meyer, *Zeits. f. physiolog. Chem.*, 1906, 46, 497; Loeb, Bock, and Fitz, *Loc. cit.*

⁴ Dodd, *Brit. Med. Jour.*, 1891, i, 849.

⁵ Schild, *Loc. cit.*

⁶ Ehrlich and Lindenthal, *Loc. cit.*

⁷ Hamilton, *Loc. cit.*

less acute cases¹ there are drowsiness, faintness, headache, unsteadiness of gait, the patient acting like a person intoxicated, and stupor; the face is flushed, then cyanotic. There are cardiac irregularity, loss of voluntary power, and extreme cyanosis. The urine is reddish brown and has the odor of bitter almonds. Coma may come on very suddenly, with symptoms resembling those of apoplexy, death being preceded by Cheyne-Stokes respiration and occasionally by convulsions.

Men engaged in industries involving the use of nitrobenzene frequently suffer from a form of chronic poisoning² in which languor, somnolence, breathlessness, blueness of the face, and sometimes failure of the sight are common symptoms. The urine is of a dark maroon color, and on warming gives the odor of the oil of bitter almonds. Adams³ described a very chronic case of poisoning extending over years in a woman who used nitrobenzene as a cleansing agent for her hands and clothing; the outstanding symptoms were fatigue, multiple neuritis, extreme indigestion, emaciation, and anemia.

Fatal Dose.—Fifteen drops of nitrobenzene have proved fatal; in another case 23 minims (1.38 c.c.) taken in seven doses during forty-eight hours caused extremely alarming symptoms. Alcohol seems to favor absorption, so that a dose not otherwise fatal may cause death when taken with alcoholic drinks. On the other hand, patients have recovered, under treatment, from 3½ ounces (105 c.c.).⁴ From ½ to 1½ drams (1.85–5.55 c.c.) would probably, under ordinary circumstances, cause death; smaller quantities would probably be fatal under some conditions, while recovery would follow much larger doses under appropriate treatment. Of 61 cases collected by Lewin, 24 (or 39.3 per cent.) died; von Jaksch⁵ placed the mortality at 20 per cent.

Fatal Period.—Death has taken place within an hour from inhalation or absorption through the skin, and within three hours after the poison was taken by mouth; in most cases it has occurred within twenty-four hours, but has been delayed forty-eight hours or even longer. In many cases coma appeared in from three to five hours, and death occurred six to eight hours later. In some cases death may be delayed for several (*e. g.*, seventeen) days (Ehlich and Lindenthal).

Treatment.—If the poison has been taken by mouth the stomach should be washed out with warm water until the water no longer has the odor of nitrobenzene; a saline purge may delay further absorption of the poison. Oils, milk, and alcohol should not be given. If the poisoning has resulted from the spilling of the substance on the clothes or from its absorption from shoes, etc., these should be immediately removed and the patient given a bath. Mild cases of poisoning recover without further treatment. A warm bath with a cold douche has proved useful, also bleeding with saline infusion and oxygen in-

¹ Sanders, *Loc. cit.*

² White, *Prov. Med. Jour.*, 1892, 11, 462.

³ Adams, *Trans. Assoc. Amer. Phys.*, 1912, 27, 503.

⁴ Cissel, *abs. Lancet*, 1894, i, 1521.

⁵ Von Jaksch, *Die Vergiftungen*, 1912, 325.

halation.¹ In severe cases bleeding and blood transfusion are indicated both by theoretical considerations and experience; marked improvement may occur immediately.²

Postmortem Appearances.—The face appears flushed and the lips livid; the superficial vessels, especially those about the throat and arms, are gorged with blood. The organs have the odor of bitter almonds. This odor may persist for several days, whereas the similar odor due to the presence of hydrocyanic acid passes off in a short time. Drops of nitrobenzene may be found in the stomach and intestines several days after death. Ecchymoses may be found in the esophagus, stomach, and duodenum. The blood is fluid and dark brown, and contains "shadows" of red corpuscles as well as distorted corpuscles.

Isolation.—By the general method of distillation with steam. The distillate is then extracted with ether. On evaporating the ether layer, the nitrobenzene is left as the residue.

A separation of the nitrobenzene may also be effected by extracting the finely divided tissue with petroleum ether. On evaporating this extract, the residue is composed of nitrobenzene and some fatty material. The latter can be removed by adding water to the residue and stirring thoroughly. The fatty substances rise to the surface, while the nitrobenzene sinks to the bottom.

Tests.—1. Two drops of liquid phenol, 3 drops of water, and a piece of potassium hydroxid the size of a pea are carefully heated to boiling in a small porcelain dish. A few drops of the fluid to be tested are added, and the boiling continued. In the presence of nitrobenzene a carmin-red ring forms on the edge of the liquid, which changes to green on the addition of concentrated calcium hypochlorite solution.³

2. On treatment with reducing agents nitrobenzene is changed to anilin,⁴ which may easily be shown by the tests given for this substance (p. 731):



A convenient method of effecting this reduction is as follows: A portion of the nitrobenzene is dissolved in warm dilute alcohol, some zinc-dust is added, and the material treated with the hydrochloric acid, a drop at a time, until there is a brisk evolution of gas. The reaction is allowed to proceed until the odor of nitrobenzene has disappeared. After the solution has been diluted with water and made alkaline, the anilin may be extracted with ether.

DINITROBENZENE

Metadinitrobenzene (dinitrobenzol, $\text{C}_6\text{H}_4(\text{NO}_2)_2$, "D. N. B.") forms, when pure, colorless crystals melting at 90° C. (194° F.). It is used in the manufacture of roburite, securite, some kinds of rifleite, and other

¹ Ames, *Loc. cit.*; Tuszewski, *Loc. cit.*

² Hindse-Nielsen, *abs. Jour. Amer. Med. Assoc.*, 1920, 75, 1530; Loeb, Bock, and Fitz, *Loc. cit.*

³ Marpurgo, *Zeitschr. f. anal. Chem.*, xxxii, 235.

⁴ Hodmann, *Liebig's Annalen*, lv, 200.

explosives, and also as a dye intermediate; most cases of poisoning have occurred in connection with its manufacture or handling in the filling of shells. Koelsch¹ considered it the most dangerous shell filler. Poisoning has also resulted from the use of roburite as an insecticide² and dinitrobenzene is stated to have been used for criminal poisoning.³ It may be absorbed through the lungs or more frequently by the skin.

Its physiologic action is similar to that of nitrobenzene, and in acute poisoning⁴ the symptoms are similar: headache, vomiting, cyanosis, loss of consciousness, convulsive movements, etc. In more chronic cases there are gastric disturbances, malaise, headache, a bluish discoloration of the mucous membranes and skin, and breathlessness, dulness of the faculties, and dark colored urine; there may be a destruction of red blood-cells,⁵ and the appearance in the blood of nucleated red blood-corpuscles; in rare cases toxic jaundice like that resulting from trinitrotoluene occurs; amblyopia⁶ due to very serious and permanent injury to the optic nerve has been repeatedly observed; also disturbances of hearing. Abortion sometimes occurs. In a few cases methemoglobin has been demonstrated in the blood spectroscopically.

Detection.—Place tin-foil into the suspected fluid and add hydrochloric acid to strong acidity; after a development of at least an hour make the fluid alkaline by caustic soda and extract with ether in a separatory funnel. The reduction produces the three phenylene diamins (o, m, and p). Any metaphenylenediamin will be found in the ether extract. Evaporate the ether. Take up the residue in a little water. Acidify a solution of sodium nitrite with dilute sulphuric acid, then add to this some of the dissolved residue. A yellow to red color is produced if it contains metaphenylenediamin (Bismarck brown—triamidophenol).

A mixture of the isomeric *dichlordinitrobenzenes* came into use during the latter part of the World War as a high explosive under the name "parazol"; this preparation causes a severe dermatitis and conjunctivitis, and also, experimentally, a secondary anemia.⁷

TRINITROTOLUENE

Trinitrotoluene ("T. N. T.," "triton," "trotyl," $C_6H_2(NO_2)_3CH_3$), a fine crystalline yellow powder, melting at 82° C. (179.6° F.), sometimes used in the form of flakes or of fused yellowish-brown lumps, is employed as a high explosive, chiefly in shell and grenades. It is also used as an

¹ Koelsch, Oeffentl. Gesundheitspf., 1919, 4, 257.

² Monks, Lancet, 1902, i, 89 (7 cases).

³ Huebner, Deut. med. Woch., 1919, 45, 1273.

⁴ Spurgin, Brit. Med. Jour., 1891, i, 801; Steiner, Korr. Bl. f. Schweiz. Aerzte, 1918, 48, 1139.

⁵ Malden, Jour. Hyg., 1907, 7, 672.

⁶ Cords, Zentralbl. f. Gewerbehyg., 1919, 7, 6; Huebner, loc. cit.

⁷ Voegtlin, Livingston and Hooper, Hygienic Lab. Bull., 1920, 126; cf. Wells, Jour. Ind. Hyg., 1920, 2, 247. Wells also discusses some of the toxic properties of some of the nitro-anilins and xylenes ("tetryl," "T. N. X.," "T. N. A."). Koelsch, Oeffentl. Gesundheitspf., 1919, 4, 257, discusses the toxicity of other nitro compounds used as explosives.

ingredient of "amatol" and "cheddite," other high explosives. It came into prominence as a toxic agent during the World War; the first cases of poisoning in England were reported in 1915, in the United States in 1917. In Great Britain, in 1916, 181 cases of jaundice due to T. N. T., with 52 deaths; in 1917, 189 cases, with 44 deaths were reported¹; it was estimated that the number of individuals coming into contact with T. N. T. was more than 50,000, so that the incidence of toxic jaundice was about 3.7 per 1000 and the mortality about 1 per 1000. But for every case of jaundice it was estimated that there were at least 30 cases showing minor symptoms. In addition, there were reported at this period 14 cases of aplastic anemia—another extreme form of T. N. T. poisoning. In 1918 only 34 cases of jaundice, with 10 deaths, were reported in Great Britain. Minot² found in an unselected group of 233 workers in T. N. T. in the United States that 83 per cent. showed blood abnormalities; Voegtlin, Hooper, and Johnson³ found in 72.5 per cent. of 237 unselected workers in a T. N. T. shell-filling plant anemia of various grades.

The poisoning occurred not in the process of manufacture, but in the various manipulations involved in the subsequent handling and in shell and grenade filling. The poison may be absorbed through the skin, the gastro-intestinal tract, or the lungs; the first channel seems to be the most important.

T. N. T. is generally held to be partially reduced in the body and to undergo condensation, and then to be slowly excreted in the urine in conjugation with glycuronic acid; this product may be detected in the urine by the Webster test⁴; severe cases of poisoning, however, may fail to show the test suggesting an inability on the part of the body to excrete the poison, or that there has been a change in the disposition of the poison in the body. Lewin⁵ believes that T. N. T. is oxidized in the body to trinitrocresol.

Action.—T. N. T. acts as an irritant at its point of entrance into the body, leading to dermatitis, gastric pain, etc. After its absorption it is believed to act upon the hemoglobin, converting it into a mixture of methemoglobin and nitric oxid hemoglobin and also hematin⁶ which cannot act as oxygen carriers; hence the symptoms of breathlessness, etc. As a sequence to the alteration of hemoglobin increased blood destruction and the phagocytosis of red cells by endothelial leukocytes occur, and there is renal irritation and the passage of dark urine. The increased blood destruction leads to increased blood formation, chiefly by the marrow; if the latter fails, anemia results, and if the marrow is

¹ Legge, Ann. Rep. Chief Inspect. Fact. and Workshops, Great Britain, for 1917, 21; Jour. Ind. Hyg., 1920, 2, 121; O'Donovan, Proc. Roy. Soc. Med., 1918, 11, 149.

² Minot, Jour. Ind. Hyg., 1919, 1, 301.

³ Voegtlin, Hooper, and Johnson, Hygienic Laboratory Bulletin No. 126, 1920; Jour. Ind. Hyg., 1921, 3, 239.

⁴ Med. Res. Com., Sp. Rep. Ser. No. 11, 1918, 16; Med. Res. Coun., St. Rep. Ser. No. 58, 1921, 49.

⁵ Lewin, Arch. exp. Path. u. Pharmakol., 1921, 89, 340.

⁶ Lewin, Loc. cit.

injured, aplastic anemia occurs. The liver may fail under increased pigment metabolism and a direct toxic action of the poison and jaundice result.

Symptoms.¹—The symptoms have been divided into two groups: irritative and toxic. Among the former are various symptoms referable to the respiratory tract: nasal discomfort, sneezing, coryza, epistaxis, tightness and pain in chest, and dry cough; smarting and watering of the eyes; frontal headache; sore throat. In some cases irritative symptoms on the part of the gastro-intestinal tract are the first to appear: bitter taste, spasmodic epigastric pain, loss of appetite, acid eructations, nausea and vomiting, constipation, then diarrhea; cramps and griping. The skin shows rashes of an eczematous type over the face and extremities, most prominent where sweating is greatest; there is intense itching. The skin and hair are stained yellow or orange (and this may be mistaken for the effects of picric acid or "tetryl"). Among the "toxic symptoms" are those attributed to alteration of the blood: pallor or cyanosis, dyspnea on exertion, dizziness, headache, fatigue, pains in the legs, drowsiness, blurring of vision; those due to renal irritation: urgency and frequency of micturition and lumbar pain; those due to degeneration of the liver: pain and tenderness in the right epigastrium.

Detailed studies² of the blood changes have yielded important results, for they show that blood abnormality frequently occurs even in the most minor grades of poisoning: fragmented or fragmenting red cells were frequently found, affording evidence of a rapid increased destruction of red cells; distinct increases of these cells indicate a considerable degree of poisoning. Among other red cell abnormalities noted were the following: polychromatophilia; Howell-Jolly bodies; stippling; increased numbers of reticulated cells, indicating increased activity on the part of the blood-forming organs. A leukocytosis and a relative lymphocytosis were common. There was a reduction in the hemoglobin percentage.

The blood changes appeared to run roughly parallel to the severity of the symptoms; when they are marked they are held to indicate too severe a poisoning for an individual to be permitted to continue his work, at least for the time being.

In the most severe cases of poisoning jaundice³ develops; this is generally held⁴ to be a true toxic jaundice due to destruction of liver by the poison and not to be of hemolytic origin, although Voegtlin and his co-workers bring forward experimental and other evidence for the view that in some cases the jaundice may in part be attributed to increased blood destruction. The jaundice is associated in its early stages with

¹ Livingstone-Learmonth and Cunningham, *Lancet*, 1916, ii, 261; cf. *Ibid.*, 1026; Putnam and Herman, *Jour. Ind. Hyg.*, 1919, i, 238; Hamilton, *Ibid.*, 1921, 3, 102.

² Minot, *Loc. cit.*; Voegtlin, Hooper, and Johnson, *Loc. cit.*, etc.

³ Compare Martland, *Jour. Amer. Med. Assoc.*, 1917, 68, 835; Pantou, *Lancet*, 1917, ii, 77; Stewart, *Ibid.*, 1917, i, 153.

⁴ Compare Medical Research Council, Special Reports Series, No. 58, London, 1921.

enlargement of the liver and later with liver shrinkage; ascites was observed in one case in which considerable shrinkage of the liver was found. Toxic jaundice appeared to occur more frequently in young adults who when attacked were very prone to die. In one series¹ 83 per cent. of the cases appeared between the fifth and sixteenth weeks of employment, but it sometimes appeared several weeks after the patients had been removed from contact with the poison; in one case there was a latent period of seven, in another of nine, months.

The striking symptoms² in such cases are obstinate constipation, abdominal cramps, tenderness in the liver region, nausea and vomiting, prostration, progressively deepening jaundice, a low muttering delirium, anuria and terminal coma. In one series 33 per cent. of recognized and notified cases proved fatal.³

At autopsy⁴ the liver shows extensive necrosis and atrophy which cannot be distinguished from acute yellow atrophy. Microscopically a great part of the liver tissue is found to have undergone complete destruction associated with a proliferation of fibrous tissue. The changes are the same as those in tetrachlorethane jaundice. There is usually an extreme degree of fatty degeneration in the kidney.

More rarely death resulted from aplastic anemia⁵ unassociated with jaundice; the symptoms included bleeding from the nose, gums, delirium, and coma; the hemoglobin may be 30 per cent. and the red cells below a million and, postmortem, aplastic bone-marrow. This form of poisoning seems always to be fatal.

Prevention and Treatment.—In addition to measures to prevent accumulation of dust the skin of the workers should be protected by proper clothing and by the substitution of mechanical for hand manipulation. The hands should be thoroughly washed after each working period; Voegtlin recommends washing with a 10 per cent. solution of sodium sulphite since this is an excellent solvent for the poison. A diet containing a liberal amount of meat was found to be beneficial in warding off jaundice in dogs and is recommended for the workers. Anemic and young individuals should be excluded from work⁶ and blood examinations should be made frequently to detect the earliest cases of poisoning.

In the treatment of cases of jaundice rest in bed is essential; the bowels should be kept open; alkalis (sodium citrate and bicarbonate by mouth, bicarbonate intravenously) are recommended.

The treatment of aplastic anemia is the same as that for pernicious anemia; the prognosis is very grave. The simple anemias usually disappear when the patient is removed from the poison.

Detection.—Trinitrotoluene is excreted in the urine as a chromogen

¹ Official Communication to Minister of Munitions, *Lancet*, 1916, ii, 1026.

² Compare Martland, *Loc. cit.*, and others.

³ *Lancet*, 1916, ii, 1026.

⁴ Martland, *Loc. cit.*; Spilsbury, *Lancet*, 1916, i, 999; Turnbull, *Proc. Roy. Soc. Med.*, 1917, 10, pt. 1; O'Donovan, *Ibid.*; Stewart, *Ibid.*; Haythorn, *Bull.*, No. 7, *Internat. Assoc. Med. Mus.*, 1918, 103; Haythorn, *Jour. Ind. Hyg.*, 1920, ii, 298; Foulerton, *Jour. Path. and Bact.*, 1921, 24, 257.

⁵ Martland, *Loc. cit.*, *Lancet*, 1916, ii, 1026.

conjugated with glycuronic acid. This substance apparently consists of a mixture of two compounds: (1) the true chromogen, which is 2-6 dinitro, 4 azoxytoluene; and (2) a substance as yet unidentified, but probably a dinitro-aminotoluene. This chromogenic substance has not as yet been isolated from the blood or organs of animals poisoned with trinitrotoluene.

Webster's Test.—If the urine of a suspected case of trinitrotoluene poisoning be shaken with ether and this ethereal solution be treated with an alcoholic solution of potassium hydroxid, no coloration will be observed unless the urine has been contaminated, from external sources, with trinitrotoluene. In this latter case a pink color will be observed, which has nothing to do with the detection of trinitrotoluene, which has been absorbed and, hence, has acted as a poison.

If, after this preliminary extraction of the urine with ether, the urine be mixed with an equal volume of 20 per cent. sulphuric acid solution and again shaken out with ether, the ether separated and washed free of acid with water, and then treated with alcoholic potash, a pink color, varying in intensity with the amount present, will appear as an evidence of the reduction derivative of trinitrotoluene.

In his later work Webster modified this test as follows: Extract the urine once with ether without previous acidification. Discard this ether extract. Acidify the urine with one-half its bulk of 20 per cent. H_2SO_4 and extract twice with ether. Wash the combined ether extracts well with water and then with dilute sodium carbonate solution to remove the acid. Dry this ether extract over anhydrous sodium sulphate. On treating this purified ether extract with alcoholic potash a beautiful blue color is obtained.¹

ANILIN

Most of the cases of poisoning by "anilin" have been due not to pure anilin, but to "anilin oil," which contains anilin, some toluidin, and frequently nitrobenzene and other benzene derivatives. Most cases are "industrial" and are caused by the absorption through the skin, especially from clothes, or by the inhalation of the vapors by workmen engaged in the manufacture or use of the substance or of its derivatives. Many have occurred in dye works; of 128 cases of industrial poisoning reported in a German dye factory, 109 were due to anilin. Many cases are reported from rubber works where anilin is, or has been, used in certain operations²; also from the use of a wash for printers' ink which had anilin as one of its ingredients and among dyers and painters³. Many cases have been attributed to the wearing of shoes dyed with anilin-containing liquids⁴ and in shoemakers working with such

¹ Med. Res. Council, 1917, No. 11, 16; *Ibid.*, 1921, No. 58, 50. See also Tutin, *Lancet*, 1918, 2, 554.

² Hamilton, Bureau of U. S. Labor Statistics, *Bull.*, 179, 1915; Harrington, *Boston Med. and Surg. Jour.*, 1918, 179, 497.

³ Birge, *Jour. Amer. Med. Assoc.*, 1914, 62, 314.

⁴ Lafidouzy and Brouardel, *Press méd.*, 1900, 2, 25; *Bull. de l'Acad. de Méd.*, 1900, 3 S., 44, 114.

preparations¹; perhaps nitrobenzene (q. v.) or certain anilin dyes were contained in some of these. Infants have been poisoned from napkins stamped with anilin hydrochlorid²; a man showed symptoms of anilin poisoning after the introduction into the ear of a very small amount of fluid containing anilin.³ Occasionally the liquid is taken internally, as for the purpose of committing suicide.⁴

Properties.—Anilin (amidobenzene, phenylamin, $C_6H_5NH_2$) is a colorless, oily, inflammable liquid, of a peculiar odor and a burning, aromatic taste; it may become brown on standing. It boils at $184^\circ C.$ ($363.2^\circ F.$); is sparingly soluble in water, but readily soluble in alcohol, chloroform, and ether. It has basic properties and forms well-defined salts. The physiologic action of anilin is very similar to that of nitrobenzene—i. e., it stimulates and then paralyzes parts of the central nervous system—but the chief effects are upon the blood.

Symptoms.⁵—The most marked symptom in anilin poisoning is a grayish-blue color of the finger-nails, face, lips, and mouth; in some cases this coloration, which is largely due to the formation of methemoglobin, is almost the only effect. Other symptoms are flushing of the face, headache, giddiness, weakness, staggering gait. The urine is dark due to oxidation products of anilin. In more severe cases there are great headache, vomiting, somnolence, small, frequent pulse, and loss of consciousness. Convulsions may occur, and then coma and sometimes death. If the case is somewhat prolonged, painful micturition,⁶ jaundice,⁷ or diarrhea⁸ may follow. The breath has an odor resembling that of coal-tar. Complete recovery may not occur for five or six weeks.

Anemia, skin eruptions, various nervous symptoms, and amblyopia have been observed among men employed for some time in anilin factories, and have been attributed to chronic poisoning by anilin.

Fatal Dose and Period.—The fatal dose and period are not known. Twenty-five c.c. (7 fluidrams) of anilin oil caused the death of a young woman in twenty-four hours⁹; in another case recovery is said to have followed the taking of 75 c.c. ($2\frac{1}{2}$ fluidounces). In Dehio's case recovery followed the ingestion of 10 grams (about 2.75 fluidrams). Smith¹⁰ reported a case in which a woman died twelve hours after taking 3 ounces (90 c.c.) of marking ink that consisted largely of anilin.

Treatment.—The patient should be brought into the fresh air, and if there is anilin on his clothes or hands, it should be removed. If the anilin has been taken per os, the stomach should be washed out and

¹ Andela and others: *abs. Therap. Monatshft.*, 1912, 26, 839; Wefers, *Apotheker Ztg.*, 1912, 27, 764.

² Rayner, *Brit. Med. Jour.*, 1886, i, 294.

³ Thomson, *Ibid.*, 1901, i, 957.

⁴ Müller, *Deut. med. Woch.*, 1887, 13, 27; Dehio, *Berl. klin. Woch.*, 1888, 25, 11.

⁵ Smith, *Lancet*, 1894, i, 89; Luce and Hamilton, *Jour. Amer. Med. Assoc.*, 1916, 66, 1441; Lintz, *Ibid.*, 1917, 68, 692; Newton, *Ibid.*, 1920, 74, 1149; Hamilton, *Jour. Ind. Hyg.*, 1919, 1, 200; Trespe, *Münch. med. Woch.*, 1911, 58, 1720.

⁶ Starck, *Therap. Monatsh.*, 1892, 6, 376.

⁷ Dehio, *Loc. cit.*

⁸ Franck and Beyer, *Münch. med. Woch.*, 1897, 44, 57.

⁹ Müller, *Loc. cit.*

¹⁰ Smith, *Loc. cit.*

saline purgatives and stimulants administered; alcohol should not be given. Bleeding followed by saline infusions or by blood transfusion is indicated in severe cases; oxygen has been recommended. The patient should be kept warm.

Postmortem Appearances.—The postmortem appearances are not characteristic. Methemoglobin is found in the blood and the odor of anilin may be noticed in the organs.

Isolation.—The general method of distillation is used, but instead of acidifying, the material is made strongly alkaline with NaOH. The anilin easily passes over into the distillate which is tested as follows. If the distillate is shaken out with ether, and this ether layer is then separated from the aqueous layer and allowed to evaporate, drops of colored anilin remain as the residue.

Tests.—The distillate is alkaline and has the characteristic anilin odor and may contain oily drops.

1. On the addition of a small quantity of a solution of bichromate of potassium to a drop of concentrated sulphuric acid that contains a trace of anilin a blue color slowly appears, which persists for many minutes and finally disappears. In the presence of more or less water the color is either green or black, according to the concentration, but under no conditions does the blue color pass rapidly through purple into red. This reaction for anilin, which is conveniently made on a white porcelain surface, involves the same reagents as are used in the principal color reaction for strychnin, and in trials for poisoning by strychnin the analyst is sure to be annoyed with the senseless questions concerning anilin, questions that could be asked only by a person who had never performed the reaction with both substances.¹

2. On the addition of a solution of calcium hypochlorite to a solution of free anilin a violet color is produced, which, under certain conditions of concentration, passes through the shades of purple into a dirty red. With a solution as dilute as 1 : 10,000 the violet color is pale or does not appear at all, but on the addition of a few drops of very dilute ammonium sulphid a rose-red color is produced, even when the original solution contained only 1 part of anilin in 250,000 parts of water.

3. To 5 c.c. of the distillate add 2 drops of chloroform and 2 c.c. of alcoholic potash solution. On warming this mixture the disagreeable and pungent odor of phenylisocyanid appears if anilin was originally present.

4. Anilin salts in great dilution yield with bromin water a flesh-colored precipitate of tribromanilin.

5. Evaporated with nitric acid it leaves a red residue.

"COAL-TAR" DYES

Undoubtedly in many of the cases in which injury has been attributed to anilin dyes the latter were not the cause of the trouble. Thus the dermatosis often seen in dyers,² printers,³ and workmen in

¹ Bejssenhirz, Liebig's Annalen, lxxxvii, 376.

² Compare Legge, Ann. Rep. Chief. Inspect. Factories, Great. Brit., 1918, 82.

³ Compare McConnell, Pub. Health Rep., 1921, 36, 979.

dye factories¹ is usually due to chemicals other than dyes or to mechanical irritation: strong acids or alkalis, intermediate products, bleaching powder, mordants, frequent scrubbing² of the hands with turpentine, alkalis, pumice or sandsoap, etc., and secondary infections. Similarly the inhalation or absorption from the skin of anilin, nitrobenzene, benzene, etc., the inhalation of the oxids of nitrogen or sulphur, of chlorin, hydrogen sulphid, hydrogen arsenid, etc., are often the cause of the symptoms of poisoning seen in dye factories.³

Many of the cases of poisoning reported from the wearing of shoes, etc., and attributed to "anilin dyes" were probably due to anilin or nitrobenzene.

Some dyes, *e. g.*, fuchsin, were formerly contaminated with arsenic, and this produced its characteristic effects upon persons who worked with such dyes. In other cases lead was present.

About 130 coal-tar dyes have been used, or have been suggested as suitable for use, in the coloring of food products; the United States, for various reasons, permit only eight dyes to be used for this purpose.⁴

The toxicity of most of the coal-tar dyes has been much exaggerated⁵; if free from poisonous contaminations, they are for the most part harmless, at least in the quantities ordinarily employed. Such dyes are often used, however, to give a natural color to sausages and other articles of food that have deteriorated or to conceal excess of fat, tendon, etc.⁶; hence many articles of food colored in this way are justly regarded with suspicion.

On the other hand, a number of dyes are unquestionably poisonous in the ordinary sense of the word, although poisoning in man, apart from local effects, is rare.

It may be said in general, however, that most of the dyes are mixtures and that it is impossible, in most instances, to determine how injurious the chemical individuals contained in them are.

Many nitro bodies used as dyes are unquestionably poisonous. Thus the potassium and sodium salts of dinitroceresol, which are used as substitutes for saffron under the names of "Victoria yellow," "Victoria orange," or anilin-orange, are more toxic than picric acid; a woman is reported to have died from 75 grains (4.88 gm.) of one of these preparations, which she had taken instead of saffron, with the object of bringing on an abortion. Severe⁷ and fatal⁸ poisoning has been reported from Martius or Manchester yellow (dinitro-alpha-naphthol).

Methylene-blue, which has been somewhat extensively used in medicine, causes, in large doses or after long-continued use, diarrhea, headache, dizziness, and delirium. Safranin is very poisonous when

¹ Compare Legge, Jour. Ind. Hyg., 1920, 2, 121; Bachfeld, Zentralbl. f. Gewerbehyg., 1920, 8, 113, 149.

² Blaschka, Deut. med. Woch., 1891, 17, 1241, 1262.

³ Hamilton, Jour. Ind. Hyg., 1919, 1, 200.

⁴ Food Insp. Decision 180, April 21, 1919; cf. Hesse, Bur. of Chem. Bull., 147, 1912.

⁵ See Georgievics, Lehrb. der Farbenchemie, 1895, 10.

⁶ Das Sanitätswesen des Preuss. Staates, 1895-97, 446, 477.

⁷ Diedrich, Zeitsch. Unters. Nahr. u. Genussm., 1905, 5, 364.

⁸ See Virchow's Jahresber., 1893, i, 445.

applied to the injured skin or subcutaneously.¹ Anilin orange, often used in dyeing feathers, has caused severe local effects upon the hands of those working with it. White² reported cases of eczematous dermatitis of the neck and face produced by wearing fur tippets colored by some dark dye.

Numerous cases of poisoning have been reported from the use of hair and other dyes containing paraphenylenediamin³ ($1-3C_6H_4(NH_2)_2$) or oxidation products (ursol, etc.) of it. The symptoms have usually been local (itching, burning, edema of the eyelids, eczema, erythema, etc.), but general symptoms resembling those of chronic anilin poisoning have been reported. The sale of hair-dyes containing this substance has long been prohibited in Germany, France, Austria, etc., but nostrums containing it are sold in the United States and have caused many cases of poisoning.⁴ Dyers using paraphenylenediamin may suffer severely from asthma-like attacks; this has been held to be an anaphylactic phenomenon.⁵

Many members of the *triphenylmethane* series of dyes have a local irritating action and may cause a chemical inflammation; the pus is sterile, as the dyes are antiseptic. Small particles of copying or indelible pencils, which are impregnated with triphenylmethane dyes, usually methyl violet, cause chemosis, edema of the lid and cloudiness of the cornea, and, if not removed, necrosis, purulent inflammation of the cornea, and staphyloma. Serious injury to the hand, etc., has resulted from the breaking off under the skin of such pencils; a slowly spreading necrosis develops, leading to a fistulous ulcer or granuloma. Erdheim⁶ has observed 23 such cases. In order to check the process it is necessary to remove, by surgical means, not only all of the foreign body, but all of the violet-stained necrotic tissue surrounding it.

Bladder Tumors in Anilin Workers.—In 1895 and again in 1906 Rehn⁷ called attention to the undue prevalence of malignant tumors of the bladder in anilin dye workers; he attributed them to the inhalation of fumes evolved in the processes of manufacture. A number of similar reports have appeared from Germany and Switzerland⁸; in 1920 Curschmann⁹ listed 177 such cases.

¹ Weyl, Zeits. f. Hyg., 1889, 7, 37.

² White, Boston Med. and Surg. Jour., 1902, 146, 269.

³ Puppe, Vierteljahresschr. f. ger. Med., 1896, 3 Folge, 12, 116 (Suppl.); Damianos, Therap. Monatsch., 1911, 25, 602; Olson, Jour. Amer. Med. Assoc., 1916, 66, 864; Thompson, Med. Rec., 1920, 97, 401.

⁴ See Jour. Amer. Med. Assoc., 1913, 60, 229; Nostrums and Quackery, Amer. Med. Assoc., 1912, 491.

⁵ Gerdon, Zentralbl. f. Gewerbehyg., 1920, 8, 183, 188, 201; Curschmann, Münch. med. Woch., 1921, 68, 195.

⁶ Erdheim, Arch. f. klin. Chir., 1914, 106, 91; Ibid., 1920, 113, 772; Wien. klin. Woch., 1919, 32, 726; cf. Ballin and Saltzstein, Jour. Amer. Med. Assoc., 1921, 76, 1333.

⁷ Rehn, Arch. f. klin. Chir., 1895, 50, 588; Verhandl. d. deut. Gesell. f. Chir., 1906, 35, 313.

⁸ Leuenberger, Beitr. z. klin. Chir., 1912, 53, 208; Lewin, Ztschr. f. Urol., 1913, 7, 282; Nassauer, Frank. Ztsch. f. Path., 1919, 22, 353; Oppenheimer, Münch. med. Woch., 1920, 67, 12; Schwerin, Zentralbl. f. Gewerbehyg., 1920, 8, 64.

⁹ Curschmann, Zentralbl. f. Gewerbehyg., 1920, 8, 145, 169.

The disease occurs in comparatively young men; in Oppenheimer's cases the men were between thirty-four and forty-seven years of age. It is at first, and for a long time may remain, latent; it may only become apparent long after (in one case seventeen years) the man has ceased to work in the factory. The earliest symptom is usually hematuria, which is often profuse; but before this appears the cystoscope may show a cystitis and perhaps ulcerations. Later appear nodules, papillomas, and villous tumors, which finally become malignant. The cancerous growth may invade the neighboring lymph-glands of the ureter or kidney or the bones of the pelvis and lower abdominal walls; in one case metastases were found in the liver and lungs. The mortality is very high.

A long list of chemicals has been suggested as the etiologic factor: naphthylamins, benzidin, naphthionic acid, anilin, toluidin, fuchsin, safranin, various black and blue colors, etc. It is interesting to note that all of these are amino compounds and Hamilton¹ has pointed out that in their production there is always the possibility of arsin being produced from the action of the acid on the scrap iron or zinc dust used in the processes of the reduction; she suggests that these tumors may in reality be due to the arsenic. Hamilton also calls attention to the work² suggesting that the soot, pitch, and paraffin tumors—the chimney-sweepers' cancer and the epithelioma of briquet makers—which have long been considered analogous to these "anilin" tumors) may be due to chronic arsenic poisoning; this interpretation, however, has been questioned.³

ACETANILID

Acetanilid (Acetanilidum, U. S. P.; "Antifebrin"), $C_6H_5NH(CH_3CO)$, occurs in colorless, crystalline laminæ, or as a crystalline powder; odorless; slightly burning taste; soluble in 190 parts of water, in 3.4 parts of alcohol, in 3.7 parts of chloroform, and 17 parts of ether at 25° C. (77° F.); much more soluble in hot water. It melts at 113° C. (235.4° F.). It is formed by substituting one H atom of the NH_2 group of anilin by the acetyl group.

The **physiologic action** of acetanilid differs somewhat in health and disease. In some forms of fever the only effect usually noticed from medicinal doses is a fall of temperature due to a narcotic action upon the hyperirritable heat-regulating centers of the brain; the fall of temperature is accompanied by perspiration. It has a similar narcotic action in certain forms of headache. The **toxic actions** manifest themselves chiefly in the formation of methemoglobin, which results in cyanosis, and in a depression of cerebral and medullary centers, which leads to collapse and failure of the respiration and circulation. With small doses the red blood-corpuscles remain intact, but large doses destroy the cells and free the methemoglobin which may lead to hem-

¹ Hamilton, Jour. Ind. Hyg., 1921, 3, 16.

² Bayet and Slosse, Bul. de l'Acad. Roy. de. Med. de Belgique, 1919, 29, 607.

³ Burkhardt, Zentralbl. f. Gewerbehyg., 1920, 8, 220.

aturia, nephritis, and jaundice. Acetanilid is excreted in man as compounds of paraminophenol in combination with sulphuric and glycuronic acids; the urine gives the indophenol reaction.

Acetanilid has some antiseptic action and was formerly applied to wounds, from which it was often absorbed and produced the usual toxic effects.

The most frequent **source of poisoning** from acetanilid has been its use as a remedy for headache; of 614 cases of poisoning reported by physicians to the U. S. Department of Agriculture, 325 cases (53 per cent.) occurred when the drug was taken without a physician's prescription.¹ Of cases reported in medical literature in recent years a large percentage (87.5 per cent. in the year 1907) has resulted from the use of proprietary preparations containing acetanilid. Among the proprietary preparations to the use of which poisoning has been attributed are "Antikamnia," "Bromo-Seltzer," "Cephalgin," "Koehler's Headache Powders," "Orangeine," "Stearns' Headache Cure," "Daisy Powders," etc.²

In a few cases it has been taken with suicidal intent.

It is noteworthy that many cases of poisoning have resulted from mixtures of acetanilid and caffeine.³ There seems to be a wide-spread belief that caffeine in some way diminishes the toxicity of acetanilid, although there is no clinical evidence for this view, and experimental work shows that the opposite is the case: that caffeine increases the toxicity of acetanilid (and also of antipyrin).⁴

Many cases of poisoning (8.7 per cent. of those reported in the medical literature up to 1907) have resulted from its external application: to burns,⁵ wounds, ulcers,⁶ inflammation of the skin, etc.

The chief **symptoms**⁷ caused by acetanilid are marked and long-continued cyanosis, great weakness, prostration, and collapse; coldness of extremities, profuse sweating; with feeble, often imperceptible, pulse; feeble, shallow respiration, unconsciousness; sometimes marked restlessness, convulsions, and delirium; sometimes persistent vomiting and dyspnea; pupils dilated, sometimes constricted. In mild cases of poisoning, cyanosis, especially marked under the finger nails, on the extremities, and lips, is often the only symptom. The oxygen capacity of the blood is lowered,⁸ and methemoglobin can be detected by the spectroscope.

In cases which survive for a few days there is a progressive destruc-

¹ Kebler, Morgan, and Rupp, Bull. 126, Bureau of Chemistry, 1909.

² See Nostrums and Quackery, Amer. Med. Assoc., 1912.

³ For example, Hemenway, Jour. Amer. Med. Assoc., 1906, 47, 2158; Smedley, Ibid., 1907, 48, 1433; Sanford and Van Wagman, Ibid., 1907, 48, 1693; Wynn, Ibid., 1907, 49, 1027.

⁴ Hale, Bull., 53, Hygienic Lab., U. S. Public Health Service, 1909.

⁵ Manasses, Internat. Med. Mag., 1901, 10, 278; Gartmann and Ball, Phil. Polyclinic, 1897, 6, 381.

⁶ Carmalt, Yale Med. Jour., January, 1896, 2, 90; See Case 4.

⁷ See also Report of Therap. Committee, B. M. A., Brit. Med. Jour., 1894, 1, 85, Case 1; Arculli, Lancet, 1921, 1, 965.

⁸ McEllroy, Jour. Amer. Med. Assoc., 1919, 73, 1927; Ellinger, Zeits. f. phys. Chem., 1920, 111, 86.

tion of red corpuscles; there may be acute nephritis, suppression of urine, and acute, progressive jaundice.¹

Many cases of chronic poisoning have been reported (in 10.7 per cent. of the recorded cases and in 7.6 per cent. of the cases reported to the Department of Agriculture); many of them result from the use of proprietary headache remedies,² others from the external application of acetanilid.³

The symptoms⁴ are great general weakness, nervous excitability, insomnia, loss of appetite, digestive disturbances, cyanosis, often extreme, but fluctuating; a secondary anemia; dyspnea on exertion; moderate leukocytosis; the blood from the finger-tip may be bluish black or of a chocolate color; heart usually enlarged, sounds feeble and has adventitious murmurs; urine dark brown, containing blood-pigments in the form of methemoglobin. A definite "acetanilid habit" is recognized; maniacal excitement has followed the sudden withdrawal of the drug.⁵

The mortality in reported cases of acetanilid poisoning has increased within recent years; from 1887 to 1890 it was only 1.6 per cent., whereas from 1905 to 1907 it was 16.6 per cent.; this has been attributed to the increase in its indiscriminate use by the public. In the 614 cases of poisoning reported to the Department of Agriculture 2.7 per cent. terminated fatally.

Fatal Dose.—It is impossible to state a probably fatal dose for acetanilid. Many of the recorded deaths have resulted from the taking of proprietary headache remedies in which other drugs, especially caffeine, may have contributed to the fatal result; in these, and in other cases, there was often a history of an already chronic form of poisoning or of some pre-existing disease. In patients with fever death has been attributed to 5 grains of acetanilid.⁶

Death was reported from a proprietary preparation containing 18 grains of acetanilid⁷; from 7.5 grains (with 1.5 grain caffeine citrate)⁸; from 60 grains⁹; in other cases from 8 to 30 grains. A boy of seven died in two hours after a third dose of 4.5 grains of acetanilid and 0.38 grain of caffeine.¹⁰

On the other hand, recovery has followed the ingestion of doses up to and perhaps beyond 120 grains.

Severe symptoms have repeatedly followed the ingestion of doses of 4 to 15 grains.

¹ See Case 2.

² Austin and Larrabee, *Jour. Amer. Med. Assoc.*, 1906, 46, 1680; Blackburn, *Ibid.*, 1767; Glazebrook, *Ibid.*, 1907, 49, 1673; Gordinier, *Boston Med. and Surg. Jour.*, 1911, 165, 198, McElroy, *Loc. cit.*

³ See Case 4.

⁴ See Case 3, Gordinier, *Loc. cit.*, Nadler, *Jour. Amer. Med. Assoc.*, 1920, 74, 1717; Shuman, *Ibid.*, 1921, 77, 526.

⁵ See Case 4.

⁶ Thomas, *Indiana Med. Jour.*, 1890, 9, 67.

⁷ Easley, *Amer. Pract. and News*, 1891, 12, 178.

⁸ Smedley, *Jour. Amer. Med. Assoc.*, 1907, 48, 1433.

⁹ Case 2.

¹⁰ Case 1.

The treatment consists in thoroughly washing out the stomach and in administering saline purgatives and stimulants (camphor, etc.). If the cyanosis and dyspnea are severe, bleeding followed by the infusion of normal saline solution is recommended. In chronic poisoning complete recovery usually follows the withdrawal of the drug.

CASES OF ACETANILID POISONING

CASE 1.—Boy aged seven; headache. Given powders, each containing $4\frac{1}{2}$ grains of acetanilid and 0.38 grain of caffeine at 9, 10.15, and 11 A. M. He became faint and at 11.45 his lips and tongue were very blue; face yellowish, eyes staring, protruding and unseeing. At 12.15 he commenced to jerk, twitch, and scream; the convulsive movements became worse and the boy died shortly before 1 o'clock.¹

CASE 2.—Man, thirty-seven; had taken 60 grains of acetanilid within a few hours. Lived eight days; frequent vomiting; general hyperesthesia; deep cyanosis of lips, gums, and extremities; rapid pulse; shallow respiration; red blood-corpuscles reduced to 1,116,000 with 30 per cent. hemoglobin; marked leukocytosis (66,450) and a large number of nucleated red cells of all sizes; temperature at first elevated, then fell to 95.5° F.; complete suppression of urine three days before death. There were acute diffuse nephritis, hemorrhage from the intestines, and acute progressive jaundice.²

CASE 3.—Woman aged twenty-five. Habitual use of acetanilid for about seven years. Cyanosis varying with amount of drug taken. Often faint and nauseated; lips and nails almost black, skin lead colored; pulse hardly perceptible; shortness of breath; cold extremities. Red blood-corpuscles 1,860,000. Cessation of the habit was followed by return to health.³

CASE 4.—Woman, fifty. For seven years had applied acetanilid to large ulcer of leg; had suffered from general nervousness, mental depression, weakness, dyspnea, cyanosis, and palpitation. Stopping the use of the drug caused maniacal excitement, proving addiction. Secondary anemia; liver and spleen enlarged; urine dark and gave test for paraminophenol. Patient recovered after gradual withdrawal of drug.⁴

Isolation and Detection.—The material under examination is extracted with strong alcohol for the removal of proteins. After evaporating the alcohol, the residue is taken up in acidified water and the acetanilid is shaken out of the acid fluid with ether or chloroform. To the residue obtained after evaporating the organic solvent the following tests may be applied:

1. Upon warming a mixture of acetanilid, chloroform, and alcoholic solution of potassium hydroxid the offensive odor of isobenzonitrile may be detected.⁵

2. Heat about 0.1 gram of the suspected substance for a minute with 1 c.c. of hydrochloric acid, and add a small quantity of a solution of calcium hypochlorite and phenol. A red color is produced which changes to a fine blue on the addition of ammonia.⁶ For other reactions and proof in the urine see Vulpus.⁷

3. If 0.1 gm. acetanilid is boiled with 1 c.c. of HCl, then allowed to cool, and 5 drops of fresh chlorin-water added, a blue color develops, and gradually dies (Rickert).

¹ Sanford and Van Wagman, Jour. Amer. Med. Assoc., 1907, 48, 1693.

² Brown, Amer. Jour. Med. Sci., 1901, 122, 770.

³ Stengel and White, Univ. Penn. Med. Bull., 1903, 15, 462.

⁴ Herrick and Irons, Jour. Amer. Med. Assoc., 1906, 46, 351.

⁵ Kottmayer, Chem. Centralbl., 1890, ii, 1030.

⁶ Zeitschrift f. anal. Chem., xxvii, 666.

⁷ Vulpus, Ibid., xxviii, 103.

4. To some acetanilid is added 1 c.c. of 0.2 per cent. potassium dichromate and 8 c.c. of sulphuric acid and thoroughly shaken; a red color develops, which changes to blue, blue-green, and finally fades.

ACETPHENETIDIN, U. S. P. (PHENACETIN), $C_9H_9(OC_2H_5)NH(CH_3CO)$

Acetphenetidin differs from acetanilid only in having an oxyethyl group in the para position. Its physiologic actions are practically identical with those of acetanilid except that they are developed more slowly; they are due to the transformation of the acetphenetidin into para-aminophenol. Acetphenetidin is less toxic than acetanilid, but the symptoms¹ of poisoning are practically identical; they are weakness, depression, collapse, cyanosis (in 34.3 per cent. of the recorded cases), with a blue-black hue of the skin and mucous membranes, formation of methemoglobin, chocolate colored urine,² dyspnea; weak, rapid heart; skin affections seem to occur more frequently than after acetanilid.³ Of 70 cases recorded in medical literature, 3 (4.2 per cent.) ended fatally; of 95 cases of poisoning collected by the Department of Agriculture, 7 (7.3 per cent.) died. In the fatal cases some pre-existing disease was usually present and it is impossible to state the fatal dose; 6 grains taken within two hours are said to have caused the death of a woman of seventy-six. Ten and 15 grains are also said to have caused death. Many cases of poisoning have been reported from taking 5 to 10 grains.

Cases of chronic poisoning are also reported⁴; also cases of addiction to the drug, with convulsive and hysteric seizures when it was withheld.⁵

Properties and Tests.—A white, glistening, crystalline powder; odorless, having a slightly bitter taste, almost insoluble in water, easily soluble in alcohol and chloroform; less readily in ether; melts at 135° C. (275° F.). Its chemical properties are similar to acetanilid.

It is excreted in urine as para-amidophenol, and can be detected as follows: The urine is acidified with HCl and decolorized with animal charcoal. Five drops of 3 per cent. chromic acid added to a few cubic centimeters of this urine yields a brown to reddish-brown color. Another portion is warmed and is then treated with 3 drops of ferric chlorid, when a reddish-brown color results.

Phosphomolybdic acid produces a yellowish precipitate with phenacetin solution and does not dissolve on heating (acetanilid precipitate dissolves). Vanadic-sulphuric acid reagent gives an olive-green color (acetanilid gives greenish-blue color changing rapidly to red). Sodium persulphate with phenacetin solution and boiling develops orange color.

¹ See Tobey, Monthly Bull. of the State Board of Health of Massachusetts, January, 1908 (fatal); Krönig, Berl. klin. Wochens., 1895, 32, 998 (fatal); Hollopeter, Med. News, 1889, 55, 335.

² Krönig, Loc. cit.

³ See West, Lancet, 1895, i, 91; Valentin, Therap. Monatsh., 1888, 2, 330.

⁴ Hirschfeld, Deut. med. Woch., 1905, 31, 66.

⁵ Davis, Amer. Med. and Surg. Bull., 1894, 7, 1490.

ANTIPYRIN

Properties.—Antipyrin (Antipyrina, U. S. P., Phenazonum, B. P., phenyl-dimethyl pyrazolon, $C_6H_5N.CO.CH.NCH_3.C.CH_3$) occurs in the form of colorless, inodorous crystals with a bitter taste, very soluble in water and alcohol. It melts between 111° and 113° C. (231.8° and 235.4° F.). The physiologic action of antipyrin is very similar to that of acetanilid; it has a narcotic action on the heat-regulating centers; it also has an analgesic action. It differs from acetanilid and acetphenetidin in not causing the formation of methemoglobin. It is excreted in the urine, where it may be detected by the ferric chlorid reaction; part is in combination with sulphuric acid.

Antipyrin was introduced into medicine as an antipyretic in 1884; between that date and 1909, 488 cases of poisoning, with 10 deaths, were reported. The U. S. Department of Agriculture collected 105 cases, with 5 deaths; in 26 of these cases the drug was taken without a physician's prescription.¹ Most of the cases of poisoning have been medicinal; in some cases an overdose was given,² but in many of them the unfavorable symptoms seem to have been dependent upon some abnormal or unusual condition of the patient. It was used for murder in one case.³ In a few cases habit formation has been reported.

Symptoms.⁴—Probably the most frequent toxic effect has been the appearance of skin rashes or eruptions⁵ often accompanied by edema⁶ and itching; these effects have usually been of brief duration.

Other symptoms have been prostration and collapse with pallor, cold perspiration, rapid and feeble pulse, and occasionally cyanosis⁷; nervous symptoms such as restlessness⁸ or convulsions, disturbances of sensation or of hearing; rarely amblyopia,⁹ vertigo, delirium,¹⁰ or coma; occasionally albuminuria. In a fatal case reported by Pollak (woman aged thirty; 17 grams of antipyrin in two and a half days) there were drowsiness, an erythematous eruption, cyanosis, cold skin, but rectal temperature 38.8° C., pulse 54 and small.

Long-continued use of antipyrin has led to a form of chronic poisoning in which skin eruptions, itching, dyspepsia, loss of appetite, drowsiness, and muscular weakness have been prominent symptoms; a form of hypersensitiveness¹¹ ("anaphylaxis"¹²) of long duration may develop.

¹ Kebler, Morgan, and Rupp, Bull. 126, Bureau of Chemistry, 1909.

² Pollak, Wien. med. Woch., 1911, 61, 1555.

³ Fulham Murder Case, Pharm. Journal and Pharmacist, 1913, 90, 325.

⁴ See Lewin, Die Nebenwirkungen der Arzneimittel, 1899, 459; also Report of Therapeutic Committee, B. M. A., Brit. Med. Jour., 1891, 1, 85.

⁵ See cases reported by Jennings, Lancet, 1888, i, 364; Short, Brit. Med. Jour., 1892, i, 1253; Seiler, Therap. Monatsh., 1902, 16, 659; Schutz, Wien. med. Woch., 1911, 61, 2771.

⁶ Blakeney, Brit. Med. Jour., 1889, ii, 85.

⁷ Eisenmann, Therap. Monatsh., 1897, 11, 233; Hayes, Brit. Med. Jour., 1896, i, 269.

⁸ Jennings, Loc. cit.

⁹ Hotz, Arch. Ophth., 1906, 35, 160.

¹⁰ Lewin, Berl. klin. Woch., 1895, 32, 727.

¹¹ Lewin, Nebenwirkungen d. Arzneimit., 1899, 459.

¹² Widal and Pasteur Vallery-Radot, Press méd., 1920, 28, 93; Compt. rend. Ac. Sci., 1921, 172, 414.

The **fatal dose** of antipyrin is not known. Death has followed, within a short time, the administration of 22 grains (1.43 gm.) to a consumptive and of 15 grains (1 gm.) to patients suffering with angina pectoris.¹ In a case of murder by antipyrin the dose was 4 drams. Alarming symptoms have repeatedly followed 10, 15, and even 5 grains.

The **treatment** is the same as in cases of poisoning by acetanilid.

Detection.—The isolation of the substance from the tissues is easily accomplished by preparing an acid aqueous extract free from proteins, as in an examination for alkaloids.² The acid solution is freed from various impurities by shaking with petroleic ether, and the antipyrin finally removed with chloroform. Upon evaporation of the chloroform antipyrin will remain in a form sufficiently pure for the following tests:

Tests.—1. Aqueous solutions of antipyrin produce a red color with ferric chlorid solution, which is discharged by mineral acids.³

2. To a small quantity of an aqueous solution of antipyrin is added a drop or two of a dilute solution of potassium nitrite acidified with sulphuric acid. The characteristic green color of nitroso-antipyrin is produced. The reaction serves for the demonstration of one part of antipyrin in 10,000 parts of water.

CANTHARIDES

Poisoning with cantharides is not common; most of the cases reported have been due to the use, by the laity, of the substance as an aphrodisiac, or as an abortifacient, or have occurred through accident.⁴ It has, however, been used for the purpose of murder. A few years ago it was proposed to treat tuberculous affections with cantharidines, and a number of cases of poisoning resulted from this practice. Severe poisoning,⁵ and even death, has resulted from its absorption from the skin, to which it had been applied as a vesicant.

Properties.—Cantharides (*Cantharis*, U. S. P., Spanish or Russian flies) is the dried coleopterous beetle, *Cantharis vesicatoria*, yielding not less than 0.6 per cent. of cantharidin ($C_{10}H_{12}O_4$), the anhydrid or lacton of cantharidic acid. The powdered drug or the tincture has usually been used, but a number of cases of poisoning have resulted from the use of salts of the acid.

Symptoms.—The symptoms are due largely to the local irritant action of the poison; this action is exerted at the point of application or at the point of excretion of the drug. Applied to the skin, cantharides or cantharidin produces redness and pain, followed by vesicles, which later coalesce to form a blister. Gangrene may result from its prolonged application to the skin. Some of the drug may be absorbed and cause poisoning.

¹ Lewin, Loc. cit.

² Consult p. 331 et seq. in section on General Principles of Toxicology.

³ Blumenthal, Jahresber. d. Chem., 1886, 1893.

⁴ Lipsitz and Cross, Arch. Int. Med., 1917, 20, 889.

⁵ Bressler, Therap. Gaz., 1890, 14, 450; Avery, Lancet, 1908, ii, 800, 1100 (2 cases).

Taken internally,¹ cantharides produces the same changes on the mucous membrane as on the skin. Vesicles form, and there is an intense burning pain in the esophagus and stomach; there may be intense thirst, but also inability to swallow. Vomiting usually occurs; the vomited matter may contain blood and shreds of mucous membrane. Bloody diarrhea with the most intense abdominal pains follows. There are weakness and a state of collapse, and death may occur in from sixteen to twenty hours after the poison is taken.

In less acute cases, and when poisoning results from absorption from the skin, the symptoms arise from the organs in which the drug is excreted—viz., the alimentary and genito-urinary tracts.² The symptoms arising from the latter organs are irritation of the bladder with a constant desire to urinate, pain referred to the penis, acute nephritis with albuminuria, scanty urine, hematuria, and rapid pulse. The inflammation of the bladder and urethra produces pain and frequently leads to priapism. In pregnant women abortion has occurred. The genital organs of both male and female are swollen and inflamed, and there is frequently, although by no means always, increased sexual desire. The nephritis may lead to death. Lipsitz and Cross, and Lipsitz, Fuerth, and Cross³ found both clinically and experimentally a marked polycythemia; this is attributed by Morgulis and Muirhead⁴ to the blood concentration resulting from loss of water by the kidneys. Chronic nephritis has been reported.⁵ Wallace and Pellini⁶ show that cantharidin produces a marked degree of acidosis, the renal injury not being an essential factor in this acidosis.

In some cases there are severe nervous symptoms with dyspnea, convulsions,⁷ trismus, and tetanus; some of these symptoms may result indirectly from the action of the poison upon the alimentary and urinary tracts.

Fatal Dose.—The actual dose of cantharides necessary to cause death is not known. Twenty-five grains (1.63 gm.) of the powdered drug have caused death; in another case recovery followed the ingestion of 42 grains (2.7 gm.).⁸ A boy of seventeen died fourteen days after taking an ounce of the tincture. A single fly which was swallowed by a child caused distressing symptoms.

Fatal Period.—Death does not usually occur until several hours or days (one to fourteen) after the poison has been taken; in the cases that are rapidly fatal the chief symptoms arise from the alimentary tract, the intense irritation of which leads to a shock-like condition; in the less acute cases death usually results from nephritis.

¹ See Jeffriss, *Brit. Med. Jour.*, 1876, i, 190, Lipsitz and Cross, *Loc. cit.*

² Clarke, *Lancet*, 1881, i, 499; Avery, *Loc. cit.*

³ Lipsitz, Fuerth, and Cross, *Arch. int. Med.*, 1917, 20, 913.

⁴ Morgulis and Muirhead, *Ibid.*, 1919, 23, 190.

⁵ Powell, *Lancet*, 1907, ii, 1296.

⁶ Wallace and Pellini, *Arch. Int. Med.*, 1921, 28, 711.

⁷ Sedgwick, *Med. Times and Gaz.*, 1864, ii, 617.

⁸ Beck, *North Amer. Practitioner*, 1891, 3, 522. See also Andrewes (*Lancet*, 1921, 2, 654), who reports persistence of symptoms, but recovery following the taking of $\frac{1}{16}$ grain of crystallized cantharidin, the equivalent of about 220 minims of the tincture of cantharides.

Treatment.—If the esophagus and stomach are not too severely inflamed, the stomach should be washed out with warm water; otherwise it may be emptied by hypodermic injections of apomorphin. Mucilaginous drinks and opiates should be given to allay the pain; oil should not be used, as the cantharidin is readily soluble in it. The irritation of the bladder is relieved by washing this organ out with warm water. Alkalis would seem to be indicated, for in animal experiments they have been found to lessen the action of the poison on the kidney.¹ The nephritis should receive appropriate treatment.

The chief **postmortem appearances** are severe gastritis, enteritis, and nephritis; cystitis and urethritis have also been observed. Vesicles may be found in the mouth and pharynx. The contents of the stomach and intestines usually contain some remnants of powdered cantharides if the powder itself has been taken; the green, shining particles are very characteristic of the drug.

Properties of Cantharidin.—The active principle is cantharidin ($C_{10}H_{12}O_4$), which has two crystalline forms: (1) right-angled, four-sided columns with four surfaces (these surfaces are beset with needles), and (2) flat tables. It is soluble in alkaline liquids. It can be isolated by acidifying the material and extracting with ether, benzene, or chloroform. It is insoluble in water. It sublimes when heated. With bases it forms crystallizable salts.

Detection.—The material under examination is heated with 8 per cent. solution of potassium hydroxid until a perfectly homogeneous mass is obtained. The fluid is allowed to cool, extracted with chloroform for the removal of various impurities, and after acidification with sulphuric acid is treated with four times its volume of 95 per cent. alcohol. The product is boiled and filtered while hot. After cooling, the liquid is again filtered and the alcohol distilled off. The residual aqueous fluid is then shaken with chloroform which takes out cantharidin.² The residue obtained by evaporation of the chloroform may be recognized by (1) ability to blister the skin (apply an olive-oil solution of the residue), (2) its crystalline form, (3) its sublimation. There are no characteristic chemical tests.

DIGITALIS

By digitalis (U. S. P.) is meant the powdered leaves of *Digitalis purpurea*, or common European foxglove, a plant that is now cultivated, or is found growing wild, in parts of the United States. Digitalis and its preparations, especially the tincture and the infusion, are used very extensively in medicine as cardiac stimulants; certain bodies reputed to be the active principles are used to a more limited extent.

The toxicity of digitalis is due to the presence of several glucosids; some of these occur also in the seeds. The most active of these is digitoxin, which occurs to the extent of 0.22 to 0.4 per cent. in leaves of average activity; it is insoluble in water. Other glucosids are digitalin,

¹ Ellinger, Münch. med. Woch., 1905, 52, 345.

² Dragendorff, Ermittlung von Giften, Göttingen, 1895, 322.

digitalein, and digitonin; the latter is almost inert physiologically. The name "digitalin" is loosely employed to designate several commercial preparations or mixtures. Thus "German digitalin" contains 50 to 60 per cent. of digitonin and only 5 or 6 per cent. of true digitalin; French or Homolle's digitalin contains a larger proportion of true digitalin; "crystallized" digitalin may consist largely of digitonin or of digitoxin. These preparations show great differences in toxicity.

Nearly all the reported cases of poisoning by digitalis have been accidental, and most of these have been due to the administration of too large medicinal doses. It was used for the purpose of murder in a very famous French case¹; it has occasionally been taken with suicidal intent or to escape military duty.



FIG. 67.—Foxglove or digitalis (*Digitalis purpurea*).

The most important **physiologic action** of digitalis is upon the heart, which is caused to contract more completely, so that the output is increased. The heart is greatly slowed (stimulation of the medullary cardio-inhibitory center); later it becomes irregular and often very rapid (increased irritability of the heart muscle); the heart finally passes into fibrillary contractions and ceases to beat.

Certain medullary centers in addition to the cardio-inhibitory are also stimulated, especially the vomiting center. The effects of digitalis upon the heart disappear very slowly; if the doses are repeated at too frequent intervals a cumulative effect, which is an important factor in cases of poisoning, results.

¹ Târdieu and Roussin, *Gaz. des Hôp.*, 1864, 37, 330; an abstract of this case is given in Maschka's *Handbuch d. Vergift.*, 1882, 495.

Symptoms.—Mild symptoms of digitalis poisoning are frequently seen during its medicinal use. These consist in nausea, vomiting, and sometimes diarrhea; headache, dizziness, imperfect vision and weakness; slow, powerful, but often somewhat irregular heart-beats (partial heart-block). When the drug is discontinued these symptoms slowly disappear.

In more severe cases¹ one of the earlier symptoms is a marked slowing of the heart; the pulse may fall to 40 or even to 25 a minute. At the same time the force of the beat is greatly increased, and the patient may suffer from throbbing of the carotids. There is nausea and very persistent vomiting, abdominal pain, and thirst; sometimes there is diarrhea. The urine is often suppressed. There are also various nervous symptoms, such as roaring in the ears, disturbances of vision, vertigo, violent headache, hallucinations, mild delirium, great prostration, and, frequently, twitchings of the muscles; these symptoms are especially marked after muscular exertion. Later the heart becomes rapid and irregular; dyspnea and collapse follow, and finally death in coma, or sometimes in convulsions. In a number of cases death has occurred suddenly from failure of the heart.

If the patient does not die, recovery is usually very slow and often interrupted by severe relapses. There are often attacks of dizziness, fainting, and irregularity of the heart.

In a case of poisoning by 6 to 7 c.c. digalen² (a proprietary preparation, 1 c.c. of which is said to contain 0.3 mg. of "digitoxin soluble Cloetta," but as to the exact nature of which there is much doubt) there was a slowing of the heart to 30 per minute, with a slow return to normal in three weeks; persistent vomiting, hiccups, diminished urine which was passed involuntarily, albuminuria, severe psychical disturbances, delirium, great restlessness, continuing for six days; disturbances of sight and hearing continuing still longer, but finally recovery.

There is a form of subacute poisoning in which the symptoms do not appear until the drug has been given for some time; this is the so-called cumulative form of digitalis poisoning. In the oft-quoted case of Kohnhorn,³ a man aged twenty-two took, in order to escape military service, about 13 grains (0.85 gm.) of digitalis in the form of pills daily. On the eleventh day he had marked symptoms of gastrointestinal catarrh and a pulse-rate of 52 a minute. He continued taking the pills until death, from sudden failure of the heart, took place on the twenty-eighth day.

It is impossible to state a **fatal dose** for digitalis or its preparations, for these vary greatly in strength; 36 grains (2.34 gm.) of the powdered leaves have caused death, while recovery has followed the

¹ See, for example, Mawr, *Lancet*, 1880, i, 166. (Case of a woman who recovered after taking nearly 1 grain (0.065 gm.) of Homolle's digitalin in the form of pills); Eckstein, *Arch. f. Kinderh.*, 1920, 68, 322.

² Heydner, *Münch. med. Woch.*, 1911, 58, 1511.

³ Kohnhorn, *Vierteljahresschr. f. ger. Med.*, 1876, xxiv, 278; see also *Lancet*, 1876, i, 582.

taking of 1 dram (3.9 gm.). Death has been caused by 1 ounce (30 c.c.) of the tincture.¹ Of the various constituents of digitalis, digitoxin is unquestionably the most toxic; in the well-known case of Koppe² $\frac{1}{30}$ grain (0.002 gm.) of digitoxin caused most severe poisoning, and it is very probable that $\frac{1}{15}$ grain (0.004 gm.) would ordinarily be fatal. A child aged one year and eleven months was very severely poisoned by about $\frac{1}{50}$ grain of Nativelle's digitalin,³ and in another case $\frac{1}{30}$ grain of a similar preparation caused dangerous symptoms in a boy of fifteen; 6 to 7 c.c. of digalen (presumably containing 1.8 to 2.1 mg. of "soluble digitoxin") caused extremely severe poisoning.⁴

The **fatal period** is usually long, death seldom occurring for a day or two; it is frequently prolonged for several (five to thirteen) days.

The **treatment** consists in thorough evacuation of the stomach and intestines and absolute rest in bed.

There are no characteristic **postmortem appearances** after digitalis poisoning; occasionally there are some indications of gastritis.

Properties of the Glucosids of Digitalis.—As stated above, the active principles of digitalis consist of several glucosids, digitoxin being the most active, digitalin much less active, digitalein uncertain both in action and in composition, digitonin almost inert, while little is known of the action of gitalin (Kraft) or of gitonin (Windaus and Schneckenberger).

Digitoxin ($C_{34}H_{54}O_{11}$) crystallizes from a mixture of methyl alcohol and chloroform in slender anhydrous prisms melting at 243° C. (469.4° F.), or from dilute alcohol in hydrated crystals melting at 145° to 150° C. (293° to 302° F.). It is insoluble in hot or cold water, very slightly soluble in ether, and readily soluble in alcohol and chloroform.

Tests.—1. Concentrated sulphuric acid dissolves it, with a greenish color, which is unchanged by the addition of bromin.

2. *Keller's Reaction.*—If a small portion of the glucosid be dissolved in 2 c.c. of glacial acetic acid containing a trace of iron (100 c.c. of glacial acetic acid and 1 c.c. of 5 per cent. ferric sulphate solution), and this solution be floated upon 2 c.c. of concentrated sulphuric acid containing a trace of iron (100 c.c. H_2SO_4 and 1 c.c. of 5 per cent. ferric sulphate), a brownish color appears at the zone of contact, this color gradually changing to green, and finally to indigo blue; after one-half to one hour the entire acetic acid layer becomes blue. Digitalin gives a cherry-red color in the upper layer of the sulphuric acid.

3. *Lafon's Reaction.*—If a small portion of the glucosid be moistened with a drop or two of a mixture of equal parts of 95 per cent. alcohol and concentrated sulphuric acid, and a drop of very dilute solution of ferric chlorid be mixed with this, an intense greenish-blue coloration is observed. Digitalin does not give this reaction.

4. *Brissemont-Derrien's Reaction.*—Dissolve a portion of the gluco-

¹ Rames, *Gaz. des Hôp.*, 1876, xlix, 756.

² Koppe, *Arch. f. exper. Path. u. Pharm.*, 1874, 3, 289.

³ Radcliffe, *Brit. Med. Jour.*, 1901, i, 338.

⁴ Heydner, *Loc. cit.*

sid in 2 c.c. of the following solution (30 c.c. of glacial acetic acid mixed with 20 c.c. of 4 per cent. oxalic acid solution and reduced to glyoxalic acid by treatment with sodium amalgam until the reaction is neutral) and float the solution on 2 c.c. of concentrated sulphuric acid. Digitoxin slowly develops a grayish-green color at the zone of contact, while digitalin strikes a cherry-red tone.

Digitalin ($C_{35}H_{56}O_{14}$) is a colorless, amorphous powder melting at 217°C . (422.6°F .). It is very sparingly soluble in water, readily soluble in hot alcohol, and very sparingly soluble in ether and chloroform.

This digitalin must not be confused with the usual commercial "digitalins," as these are mixtures of the various glucosids of digitalis. Thus German digitalin (digitalinum purum) consists of 50 to 60 per cent. of digitonin, 5 to 6 per cent. of true digitalin, and the remainder of the other glucosids. French digitalin (Homolle's digitalin) consists mainly of true digitalin. Nativelle's crystallized digitalin is largely digitoxin, while Merck's crystallized digitalin is mostly digitonin.

Tests.—1. Concentrated sulphuric acid colors pure digitalin orange yellow. This solution soon becomes blood red, changing to cherry and then violet on the addition of a little bromin-water. Instead of the bromin one may use sodium hypobromite solution, a drop of nitric acid, or of ferric chlorid solution. Indeed, on standing for an hour or so, the violet coloration will appear without the addition of any oxidizing agent other than the sulphuric acid.

2. With Keller's reaction (see above) digitalin gives a cherry-red color at the zone of contact, the lower layer of the acetic acid solution being light yellow, changing to brownish.

Digitonin ($C_{54}H_{92}O_{28}$ or $C_{55}H_{94}O_{28}$) is classed with the saponins and crystallizes in colorless needles or in thick, warty masses melting at 235°C . (455°F .). It is sparingly soluble in cold water, more readily in hot, to an opalescent solution which foams on agitation. It is only slightly soluble in absolute alcohol, ether, or chloroform.

Tests.—1. Concentrated sulphuric acid dissolves it with a red color, which is intensified on the addition of a drop of bromin-water, although the color is not changed to violet as is that with digitalin.

2. Concentrated hydrochloric acid gives a colorless solution which, after heating or on long standing, becomes yellow and finally reddish-violet, with a slight greenish fluorescence. Digitalin dissolves in concentrated hydrochloric acid with a golden-yellow color, which changes to violet-red on heating. On heating digitoxin with concentrated hydrochloric acid a greenish or brownish-green color is obtained.

3. If some of the digitonin be dissolved in alcohol and treated with an alcoholic solution of cholesterol, a crystalline precipitate of digitonin cholesterid is formed.

Isolation and Detection.—At the present time little or nothing is known as to the absorption or elimination of these glucosids. Certain it is that none of these active principles have been detected in the urine, blood, or internal organs, with exception of the gastro-intestinal tract, in cases of poisoning with digitalis. Special attention should,

therefore, center upon the examination of the vomitus and contents of the stomach and bowels and, even here, one may have great difficulty in detecting evidence of poisoning by digitalis.

While digitoxin and digitalin in the pure form are not appreciably soluble in water, yet the presence of digitonin and of digitalein brings about the suspension of the important glucosids in the menstruum employed. The identification of the individual glucosids is very complicated owing to the difficulty of separating them one from the other. However, one may obtain a sufficient number of tests to assure him of the presence of such substances in extracts of the contents of the stomach and bowels. Examination of the organs, urine, and blood would seem to be a more or less useless proceeding in the present state of our knowledge.

In the extraction of the glucosids from the gastro-intestinal contents follow the usual process of isolation of the alkaloids (see p. 52). Digitoxin and, to a less extent, digitalin and digitonin will be obtained by extraction of the acid aqueous extract with chloroform. Separation of the chloroform and evaporation of it will yield a residue to which the above tests for digitoxin and digitalin may be applied.

Physiologic Test.—It is very important to apply the physiologic test¹ to the suspected material. This is best done with frogs. The heart is exposed, the beats counted, and then 1 or 2 mg. of the suspected glucosid, in solution in alcohol of not over 20 per cent. strength, is injected into a lymph space. If the material belongs to the digitalis series, the heart will become slower, will empty itself more completely at each systole, and dilate less during diastole, until it finally stops in systole. This test should be carefully controlled by similar ones with known quantities of digitalis under the same experimental conditions.

STROPHANTHUS

Strophanthus (U. S. P.), the physiologic action and uses of which are very similar to those of digitalis, occasionally causes severe² or fatal³ poisoning; the symptoms are similar to those of digitalis poisoning, but the course is more rapid. In Neumann's case, in which a woman who had taken small doses of the tincture for three days took 2.5 gm. of the tincture at one dose, there was vomiting in a quarter to a half-hour, double vision, amblyopia, headache; persistent vomiting for several days, irregular pulse, but finally recovery.

A number of fatalities have resulted from the intravenous injection of strophanthin,⁴ a glucosid obtained from strophanthus, death occurring within a few minutes or a very few hours and frequently from doses of less than 1 mg.; in a number of these cases there was a history of the patient having taken digitalis a short time previously. There are also

¹ See Tardieu and Roussin, *Gaz. des Hôp.*, 1864, 330; Fühner, *Nachweis u. Best. v. Giften auf biol. Wage.*, 1911; U. S. P., 1916, ix, 606.

² Pollak, *Wien. med. Wehnschr.*, 1911, 61, 1555. Neumann, *Therap. Monatsh.*, 1907, 21, 215.

³ Fürbringer, see *Berlin klin. Wehnschr.*, 1888, xxv, 115.

⁴ See Rahn, *Deut. Arch. f. klin. med.*, 1920, 133, 74 (25 cases).

considerable variations in the composition of the available preparations of strophanthin.

Properties of Strophanthin (U. S. P.).—Strophanthin ($C_{40}H_{66}O_{19} + 3H_2O$) is the active principle of *Strophanthus kombe*. It is a white or yellowish crystalline powder which melts in its water of crystallization at about $158^{\circ}C.$ ($316.4^{\circ}F.$). If heated *in vacuo* to $80^{\circ}C.$ ($176^{\circ}F.$) it loses its water of crystallization, the anhydrous substance melting at 178° to $179^{\circ}C.$ (352.4° to $354.2^{\circ}F.$). It is very soluble in water and in diluted alcohol, less soluble in dehydrated alcohol; nearly insoluble in chloroform, ether, or benzene. Its solutions are neutral to litmus and are dextrorotatory.

Isolation.—An acid aqueous extract of the material under examination is prepared as in an examination for alkaloids. The aqueous fluid is freed from various impurities by shaking with benzene, and the strophanthin finally removed by shaking with amyl alcohol. Evaporation of the solvent leaves the residue, which may be tested by the following reactions:

Tests.—1. Treated with concentrated sulphuric acid strophanthin turns emerald green, changing to brown. When warmed with the acid the green color changes to violet shades and finally becomes black.

2. Add a trace of ferric chlorid solution and a few mils. (c.c.) of sulphuric acid to an aqueous solution of the suspected residue. A reddish-brown precipitate is produced, which turns emerald green after one or two hours.

3. Sulphuric acid containing a little phenol gives a violet color changing to green. Fröhde's and Mandelin's reagents yield the same colors.

4. Strophanthin gives a red color when treated in turn with a solution of sodium nitroprussiate and an alkali.

5. Tannic acid yields a precipitate with strophanthin, which dissolves in excess of the reagent.

Physiologic Test.—Perform the physiologic test on a frog's heart as outlined under digitalis. The heart is stopped in systole by as little as $\frac{1}{100}$ mg. of strophanthin.

OLEANDER

The leaves and bark of the common ornamental shrub, *Nerium oleander*, contains two or more active principles belonging to the "digitalis series"¹; a number of cases of poisoning, especially among children, are reported. The symptoms² have been vomiting, abdominal pains, vertigo, convulsive movements, insensibility, small, very slow pulse, and in some cases epileptiform convulsions, followed by coma and death. In cases that have recovered the pulse-rate has remained as low as 40 a minute for five days.

¹ Schmiedeberg, Arch. exp. Path. u. Pharmacol., 1883, 16, 149; Straub, Ibid., 1917, 82, 327.

² See Therap. Gaz., 1888, 12, 452; Pieszezek, Arch. Pharmacie, 1890, 228, 352 (many fatal cases); Barisien, Arch. de méd. et pharm. mil., 1898, 31, 227; Wateff, Deut. med. Woch., 1901, 27, 801.

COTTON-ROOT BARK

Cotton-root bark, which has long had the reputation among the negroes of the South of being an abortifacient, has been used to some extent as an emmenagogue. It was supposed to have some of the physiologic actions of ergot; these are, however, extremely slight.¹ A few cases of poisoning have been reported²; the symptoms were a rapid, weak pulse, dilated pupils, shallow respiration, great muscular relaxation, and sometimes abortion; 4 ounces (120 c.c.) of the fluidextract caused severe symptoms.³

MALE FERN

Male fern (*Aspidium*, U. S. P., the rhizome of *Dryopteris filix-mas* or of *D. marginalis*) yields an extract which is official under the name of *Oleoresina aspidii*. The active principles of this resin seem to be a number of neutral and acid bodies (filicic, flavaspidic acids, etc.), derivatives of butyric acid and phloroglucinol, etc.⁴

Male fern is used in medicine to destroy or remove from the intestine tapeworms and hookworms, and most cases of poisoning have resulted from such use. As a rule, the drug passes through the bowel without causing any effects except the death or expulsion of the worm, but sometimes when large quantities are administered or when some unknown conditions favor the absorption of an unusually large amount of the active constituent, severe and even fatal symptoms have appeared. One of the conditions that have been thought to increase the absorption of the poison has been the administration of castor oil as a purgative with or after the administration of the male fern⁵; the castor oil is thought to dissolve the filicic acid, which is very toxic, and so increase its absorption. Whether or not this is the correct explanation, it seems to be true that in many cases of poisoning castor oil had been given.

The symptoms of poisoning by male fern have been due in part to its local irritating action upon the stomach and intestines and in part to the effects of stimulation and depression of the central nervous system. The chief symptoms have been vomiting, purging, acute abdominal pain, muscular weakness, confusion, and somnolence, with twitching of the muscles or slight convulsive movements, headache, fever, dyspnea, collapse, coma, and death. In some cases, especially in children, violent convulsions have occurred.⁶ The urine has contained sugar, albumin, and blood. Icterus has often been observed, especially in the less severe cases; this has been attributed to duodenal catarrh, but may have been due to an increased destruction of the red blood-corpuscles in the

¹ Eckler, Lilly Scientif. Bull., 1920, Ser. 1, No. 10, 349.

² Seeds, Trans. Texas State Med. Assoc., 1875, 7, 211.

³ Blakeley, Med. News, 1896, 68, 416.

⁴ See New and Non-official Remedies, 1921.

⁵ Poulsson, Arch. f. exper. Path. u. Pharm., 1892, 29, 1; Sidler-Huguenin, Correspondenzbl. f. Schweiz., Aerzte, 1898, 28, 513; a full bibliography is given with the latter paper. See also Magnus-Levy, Berl. klin. Woch., 1911, 48, 561 (poisoning by a proprietary preparation); Schotten, Münch. med. Woch., 1914, 61, 2165.

⁶ Eich, Deut. med. Woch., 1891, 17, 969.

liver.¹ Twelve of 78 cases of poisoning collected by Sidler-Huguenin ended fatally.

One of the most serious symptoms in poisoning by male fern has been blindness, either permanent or temporary. In 78 cases of poisoning collected by Sidler-Huguenin,² 18 of the patients became permanently blind in both eyes, while 15 became blind in one eye. Others became blind temporarily or there was permanent impairment of the vision. The lesion was atrophy of the optic nerve.

Fatal Dose and Period.—Children have died from 1 or 2 drams (3.7 or 7.4 c.c.) of the oleoresin of male fern. The fatal dose for adults has varied from 5 or 6 drams (18.5 to 22.2 c.c.) to 1½ ounces (4.5 c.c.),³ but in one case it followed the administration of a little over 1 dram (3.7 c.c.).⁴ Death has occurred in from six to twenty hours.⁵

Treatment.—In cases of poisoning, fats and oils are contraindicated; mucilaginous drinks and stimulants should be given after evacuation of the stomach and bowel.

Postmortem Appearances.—The stomach and intestines have been found congested and swollen and sometimes covered with small ecchymoses.

Isolation and Detection.—The poisonous principle is extracted by ether. It seems to be the ethereal oil together with filicic acid. The latter when saponified yields butyric acid and phloroglucin. For identifying male fern the saponified ethereal extract is tested for butyric acid and for phloroglucin. The latter tinges a pine splinter, moistened with HCl, red.

SANTONIN

Santonin (Santoninum, U. S. P., $C_{15}H_{18}O_3$), a lactone of santoninic acid, is contained in santonica or levant wormseed; the latter are the unexpanded flower-heads of *Artemisia pauciflora*. Santonin occurs as colorless prisms or a crystalline powder, odorless, and nearly tasteless, but developing a bitter taste; very slightly soluble in water, soluble in alcohol. It melts at 170° C. (338° F.).

Santonin is used almost exclusively as an anthelmintic to remove round worms from the intestine, and most cases of poisoning have occurred from its medicinal use or from its use by the laity. The most common symptom of the general action of the poison is the production of xanthopsia, or "yellow sight"⁶—objects that are brightly illuminated have a yellow tinge—and there are often other disturbances of color vision. This effect rarely continues for twenty-four hours, al-

¹ Grawitz, Berl. klin. Woch., 1894, 31, 1171.

² Sidler-Huguenin, Loc. cit.; cf. Lewin and Guillery, Wirk. Arzneimitt. u. Gift. a. d. Auge, 1905, 2, 319; Uhthoff in Graefe-Saemisch Handbuch, 1907, 11; Harnack, Münch. med. Woch., 1912, 59, 1941.

³ Coghill, Lancet, 1882, ii, 530; Editorial, Boston Med. and Surg. Jour., 1882, 107, 478.

⁴ Paltauf, Prag. med. Woch., 1892, 17, 43.

⁵ Eich, Loc. cit.

⁶ Rey, Therap. Monatsch., 1889, 3, 532; see Rose, Virchow's Arch., 1859, 16, 233; 1859, 18, 15; 1860, 19, 532; 1861, 20, 245; 1863, 28, 30.

though in one severe case of poisoning complete blindness lasted for nearly a week. Occasionally there are disturbances of the sense of taste, smell, and hearing. The symptoms¹ following the absorption of larger doses are due to changes in the central nervous system; they may begin within a few minutes.² There are headache, dizziness, trembling, unsteady gait, dilated pupils, clonic convulsions,³ loss of consciousness; there is a fall of body temperature. The convulsions may continue for several days, or the patient may early pass into a condition of stupor. These nervous symptoms are often preceded by abdominal pain and vomiting. Other symptoms observed have been perspiration, skin eruptions, edema of the skin, fever, and symptoms of irritation of the urinary passages—strangury, hematuria, and albuminuria. There is a tendency to a cumulative action on the part of the drug, as the latter is excreted slowly by the kidneys. The urine is yellow and may be diminished in quantity.

Fatal Dose and Fatal Period.—Nearly all cases of poisoning have occurred among children. Children from five to six years old have died in from thirty-five minutes to fifteen hours after taking 6 grains (0.39 gm.) of santonin.⁴ A child of three and a half years was severely poisoned for two days by $1\frac{1}{2}$ grains (0.1 gm.), but recovered; another child of four recovered after taking 4 grains (0.26 gm.). These and similar cases show⁵ that 2 or 3 grains (0.13–0.195 gm.) of santonin would be dangerous, and probably, at times, a fatal dose, for most children of from four to seven years of age. Adults have recovered from doses of from 8 to 15 grains (0.52–1 gm.). One-third of an ounce (10 gm.) of the crude drug caused the death of a child of ten years in two days.⁶

The **treatment** should consist in thorough evacuation of the stomach and bowels; ether, chloroform, or chloral hydrate may be necessary to control the convulsions. In case of collapse, warm baths with cold affusions are recommended. There are no characteristic **postmortem appearances**.

Isolation.—Neumann has shown that santonin is partly decomposed in the body, giving rise to two substances, one of which appears in the urine and produces a red color with aqueous potassium hydroxid, while the other remains in the feces and loses its red color when treated with alkalis. Rhubarb will also yield a red color in the urine when made alkaline. If this red colored urine is now digested with zinc dust, santonin urine fades, rhubarb urine remains red. Any undecomposed santonin, as well as these decomposition products, may be recovered by either of the two following processes:

¹ See, for example, Blinn, *Therap. Gaz.*, 1887, 11, 497.

² Kilner, *St. Thomas' Hosp. Rep.*, n. s., 1880, 10, 246.

³ A number of cases of santonin poisoning in which convulsions occurred are cited by Binz, *Arch. f. Exper. Path. u. Pharmakol.*, 1877, 6, 308.

⁴ See Grimm, *Schweiz. Zeitschr. f. Med.*, etc., 1852, 492; Kilner, *loc. cit.*; Edworthy Case, *Pharm. Jour. and Trans.*, 3 S., 1878, 8, pt. ii, 996.

⁵ Forshheimer, *Therap. of Inter. Dis.*, 1913, 3, 251; Chassevant, *Jour. de méd. de Paris*, 1914, 26, 130; Magri, *abs. Jour. Amer. Med. Assoc.*, 1914, 68, 892.

⁶ Linstow, *Vierteljahresschr. f. ger. Med.*, 1874, xxi, 80.

1. The material under examination is made into a thin paste with very dilute sodium hydroxid and digested at 30° C. (86° F.) with three times its volume of 96 per cent. alcohol for twenty-four hours. The liquid is filtered, the alcohol distilled off, and the aqueous alkaline fluid is shaken out with benzene. As long as the liquid is alkaline, santonin will not be taken up by benzene, and various impurities may thus be removed. The santonin can finally be removed with chloroform or benzene after the aqueous fluid has been acidified with hydrochloric acid.

2. The material under examination is digested for several hours on the water-bath with milk of lime, and after filtration the alkaline fluid is treated with benzene as given above.¹

Tests.—1. The material is placed on a watch-glass and exposed to the sunlight for a day or two.² On adding a drop of alcoholic solution of potassium hydroxid a characteristic red color is produced.

2. Neumann claims that the following modification of the Lindo³ test will show the presence (0.0001 gm.) of santonin. A minute quantity of the suspected substance is warmed with a mixture of two volumes of concentrated sulphuric acid and one volume of water until a yellow color appears, when the material is allowed to cool and a few drops of 0.066 per cent. solution of ferric chlorid are added. On heating a second time a fine violet color appears.

3. When fused with potassium hydroxid, santonin imparts a red color to the mass.

4. Alcoholic solution of santonin plus 2 drops of alcoholic furfural solution and 2 c.c. of sulphuric acid warmed on a water-bath gives a red color, changing to violet and to blue.

5. If alcoholic solution of KOH is added and warmed, a beautiful red color develops.

VEGETABLE PURGATIVES

A number of drugs of plant origin are used extensively in medicine as purgatives and occasionally give rise to poisoning. Most of the cases of poisoning are accidental, although some have been due to the use of the drugs for criminal purposes—for committing murder or for securing abortion. These substances differ widely in their chemical properties, but their physiologic action is essentially the same. In small doses they simply hasten the normal movements of the intestines, while larger quantities cause all the symptoms of acute gastro-enteritis. After poisonous doses there is violent purgation, accompanied by colic, griping pain, and tenderness in the abdomen; shock, collapse, and death may follow. Some of these drugs also cause local irritation when applied to the skin.

These purgatives may be divided into three classes, according to their chemical properties: (1) Purgative oils; (2) purgatives of the anthracene series; (3) the jalapin group.

¹ Neumann, *Jahresber. der Chem.*, 1884, 1645.

² Neumann, *Loc. cit.*

³ *Chemical News*, 1877, xxxvi, 222.

PURGATIVE OILS

Croton Oil.—Most cases of poisoning¹ with croton oil have been due to accident, as when preparations intended for external use have been swallowed,² or to the taking of too large medicinal doses. In rare cases it has been used for criminal purposes; thus strawberries³ and cherries have been filled with croton oil and given for murderous purposes, or small doses have been given for a long period with the hope of causing death by setting up a chronic inflammation of the intestines.⁴ Death has also resulted from its administration in whisky as a practical joke.⁵ A few cases of poisoning have resulted from the eating of the seeds of the plant.

Croton oil (*Oleum tiglii*, U. S. P.) is a fixed oil expressed from the seeds of *Croton tiglium*; it contains about 10 per cent. of "croton resin," the active component.

Symptoms.—When taken internally, ordinary croton oil causes burning and irritation in the mouth and throat, salivation, and vomiting. There are severe abdominal pain and profuse, often bloody, diarrhea, accompanied by much straining and tenesmus. The body is covered with cold perspiration, the pulse is small and irregular, the respiration slow and shallow; there are cyanosis and a fall of temperature. Finally there are delirium and collapse, and death from failure of the respiration. Occasionally death occurs without purging.⁶ When applied to the skin, croton oil causes burning, redness, and vesication; the vesicles may later contain pus. One-tenth of a milligram of croton oil applied to the tongue causes intense burning, continuing for hours. In chronic poisoning there has been extreme emaciation.

Fatal Dose and Period.—Some specimens of oil are more toxic than others; thus old specimens seem to be more toxic than fresh samples. This fact, as well as the circumstance that in most cases of poisoning some of the oil is returned in the vomit, makes it very difficult to determine the fatal dose.⁷ One or 2 drops have caused severe poisoning, while 20 drops have caused death; a child of thirteen months died in six hours from $2\frac{1}{2}$ minims.⁸ On the other hand, recovery has occurred after 1 dram and even after 1 ounce (30 c.c.) of the drug.⁹ The medicinal dose is from $\frac{1}{3}$ to 1 minim. Death has occurred in four hours from $2\frac{1}{2}$ drams (9.25 c.c.); in another case, after a dose of less than a teaspoonful, death was delayed for three days. Death usually occurs within twelve hours. One-fourth of an old seed when chewed¹⁰ has caused severe poisoning; a single seed is said to have caused death. The

¹ Hirschheydt, *Dorp. Arb.*, 1890, iv, 5.

² Augé, *Lancet*, 1870, i, 553; Adam, *Edinburgh Med. Jour.*, 1856, i, 932.

³ Mayet and Hallet, *Ann. d'hyg. pub.*, 1871, xxxv, 192.

⁴ Homicide case, *Jour. Amer. Med. Assoc.*, 1903, 41, 172.

⁵ Ellis, *Amer. Jour. Med. Sci.*, 1874, lxxvii, 436.

⁶ Ellis, *Loc. cit.*

⁷ Brydon, *Edinburgh Med. Jour.*, 1861, vii, 134.

⁸ *Med. Times and Gaz.*, 1870, ii, 466.

⁹ Bunting, *Boston Med. and Surg. Jour.*, 1868, lxxviii, 294.

¹⁰ Schulz, *Therap. Monatsh.*, 1889, iii, 89.

seeds contain, in addition to croton oil, poisonous toxalbumins. These are said to be especially abundant in fresh seeds.

The **treatment** consists in the thorough evacuation of the stomach by the stomach-tube or by the hypodermic injection of apomorphin. Demulcent drinks and morphin should be given to allay the pain. Cardiac and respiratory stimulants may be necessary.

Postmortem the mucous membrane of the alimentary tract is usually found reddened and swollen, and sometimes detached in places; hemorrhages may be found in the intestines. In some cases practically no changes have been found.

Detection.—The contents of the stomach and bowels, vomited matter, food, or other material to be tested should be finely subdivided, slightly acidified, if necessary, with tartaric acid, and repeatedly extracted with ether. The latter upon evaporation leaves as a residue any croton oil that may have been present in the material tested, together with other fatty substances soluble in ether. The residue may be tested for the presence of croton oil by rubbing a little of it on the inside of the arm and observing the eruption produced; and also by administering a small quantity to a cat, dog, or other lower animal and noting the gastro-intestinal effect. There are no conclusive chemical tests for croton oil in the small quantity in which it may usually be extracted from the contents of the stomach, and we are obliged, therefore, to rely upon physiologic experiments.

Castor oil (*Oleum ricini*, U. S. P.) seldom, if ever, leads to severe poisoning.

The seeds from which castor oil is obtained contain the highly poisonous toxalbumin ricin, a body that has received much attention in studies on immunity; animals may readily be immunized against it. Ricin does not pass into the castor oil, but severe and fatal cases of poisoning may be caused by it when the castor-oil seeds are eaten: the press cake remaining after the (cold) extraction of the oil is also poisonous and men working with it may suffer from inflammation of the eye. Stillmark¹ and Beauvisage² collected, up to 1894, 150 cases of poisoning, 9 of which were fatal. The symptoms, which at times began within forty-five minutes, but were usually delayed for some hours, have been compared to "ptomain poisoning"; there were vertigo, great weakness, and persistent vomiting; in most cases there was diarrhea, with rice-water, sometimes bloody, evacuations and tenderness and pain in the epigastric and umbilical regions. Later there were symptoms of severe collapse; small, frequent, barely perceptible pulse, cold perspiration, and death in from three to five or more days. In rare cases icterus, in others convulsions, were observed. In 16 cases of non-fatal poisoning observed by Edson³ there was persistent vomiting, but no catharsis; the patients were for the most part children under six. It is thought that

¹ Stillmark, Kobert's Arbeiten d. pharmakol. Inst., Dorpat, 1889, 3, 111.

² Beauvisage, Tox. des grains de ricin, 1894; cf. Wood, Australian Med. Jour., April, 1911, 16, 176 (10 cases).

³ Edson, Brooklyn Med. Jour., 1888, i, 131.

3 or 4 seeds were eaten by each. Severe poisoning has resulted from the eating of 1 or 2 seeds.¹

The severity of the symptoms seems to be somewhat independent of the number of seeds taken. Death followed, in six days, the eating of 2 seeds²; in another case death occurred in forty-six hours after eating 3 seeds; on the other hand, recovery followed the eating of 8 or 10 and of 25 or 30 seeds,³ or even, it is reported, of 100 seeds.⁴

Postmortem.—The mucous membrane of the stomach and intestine was found to be strongly injected, swollen, semidetached, and easily torn; there were numerous small hemorrhages. In animals innumerable ecchymoses in the great omentum occurs; also small foci of necrosed tissue in the liver, spleen, and other organs.

Detection.—The poison, even in great dilution, may be detected by its power to cause agglutination of red blood-corpuscles.

THE ANTHRACENE PURGATIVES

The purgatives—aloes, rhubarb, senna, frangula, and cascara sagrada—contain glucosids yielding emodin and other derivatives of anthraquinon ($C_{14}H_8O_2$), and to these is due their purgative action; the latter is exerted chiefly in the large intestine. The only one of importance toxicologically is aloes.

Aloes (U. S. P.) is the inspissated juice of the leaves of various species of aloe; the active principles are pentosids, called aloins, of which there are several varieties. Poisoning with aloes has resulted from the use of too large medicinal doses and from its use by the laity as an abortifacient.⁵ Abortion has followed the administration of aloes as a purgative to pregnant women.⁶ The chief symptoms are colic, abdominal pains, purgation, and tenesmus; the stools usually contain blood. It is said to have a specific action upon the uterus.

The fatal dose is placed at from $\frac{1}{3}$ to $\frac{2}{3}$ ounce (10–30 gm.).

Rhubarb (Rheum, U. S. P.) causes, in large doses, gastritis and enteritis, and in certain susceptible individuals skin eruptions.⁷

JALAPIN AND ELATERIN PURGATIVES

This group consists of a number of very active purgatives the action of which is chiefly exerted, or which begins, in the small intestine; all, with the exception of podophyllum, act promptly (one to three hours). The active principles, so far as they are known, consist of resinous bodies, often of a glucosidal nature, acid anhydrides, and glucosids; colocynth contains an alkaloid also. The most important members are colocynth, elaterin, gamboge, jalap, podophyllum, and scammony.

¹ Burroughs, Brit. Med. Jour., 1903, ii, 836; Gullen, Ibid., 1905, i, 988; Marsden, Ibid., 1299; Wrightson, Ibid., 1312.

² Meldrum, Brit. Med. Jour., 1900, i, 317.

³ Hutchinson, Ibid., 1155.

⁴ Bispham, Med. News, 1903, 82, 809.

⁵ Hedren, Vierteljahresber. f. ger. med., 29, Suppl. 1905, 43 (6 cases).

⁶ "C," Med. Rec., 1876, 11, 276; Heitzmann, Wien. med. Woch., 1896, 46, 222.

⁷ Goldenburg, New York Med. Jour., 1889, 50, 652; Litten, Therap. Monatsh., 1890, 4, 606.

Jalap and scammony owe their activity largely to the glucosids—jalapin (convolvulin, jalapurgin) and scammonin.

The drugs are often used in the form of resins or of extracts; some of them are contained in most of the purgative pills. The *Pilulæ catharticæ compositæ* (U. S. P.) contain colocynth, gamboge, jalap, scammony, and also aloes, calomel, and cardamom. Death has resulted from the excessive use of proprietary pills containing various drugs belonging to this group¹; in a case reported by Taylor such pills were used for the purpose of committing murder.

The action of all these substances is very similar; the symptoms following an overdose are vomiting, abdominal pain, violent purging, tenesmus, followed by great weakness, collapse, and death.

Colocynth (bitter apple), the fruit of *Citrullus colocynthis* (family cucurbitaceæ), contains several resinous bodies and an extremely bitter alkaloid.² A number of deaths have followed large doses of colocynth; it has often been used as an abortifacient.³ Poisoning has resulted from the inhalation of the powdered drug.⁴ Macht⁵ considers colocynth to be the poison referred to in II Kings, iv, 38-41.

The **symptoms** are the usual ones of gastro-intestinal irritation. There are also at times evidence of irritation of the kidneys, and in fatal cases deafness, delirium, prostration, arrhythmic pulse, and collapse.

The **fatal dose** and **period** have varied greatly. A few deaths have been reported from 15 to 30 grains (1-2 gm.).⁶ Recovery followed 75 grains (5 gm.),⁷ also 3 drams (11.7 gm.) and 2 drams (7.8 gm.); in the latter case the woman was pregnant, but abortion did not occur.⁸ A woman died in twenty-four hours after taking 1½ teaspoonfuls of the powder; in another case death did not occur until some time after forty hours after taking an unknown amount of the drug.⁹

Detection.—The isolation of colocynthin from the tissues is attended with some uncertainty. Tidy failed to find the poison in the case of a human being, but Dragendorff and Johansson¹⁰ isolated it from the bodies of poisoned cats. The substance is colored first brown, then red, by Fröhde's reagent, while Mandelin's reagent (0.5 per cent. solution of ammonium vanadate in sulphuric acid) produces a transient blood-red color.

Elaterin (Elaterinum, U. S. P.) is a neutral principle obtained from a substance (elaterium) deposited by the juice of the fruit of the squirting cucumber (*Ecballium elaterium*). It is an extremely active purgative, the U. S. P. dose of which is $\frac{1}{20}$ grain (3 mg.). Elaterium

¹ Paltauf, Wien. med. Presse, 1887, 28, 579.

² Power and Moore, Trans. Chem. Soc., 97, 99, 1910.

³ Everitt Case, Pharm. Jour. and Trans., 3 S., 1878, 8, pt. 2, 1035.

⁴ See Jansen, Therap. Monatsh., 1889, 3, 39.

⁵ Macht, Johns Hop. Hosp. Bull., 1919, 30, 38.

⁶ Querleux, Arch. de Méd. et Pharm. milit., 1909, 53, 276.

⁷ Roe, Lancet, 1913, i, 1527.

⁸ Rolfe, Boston Med. Surg. Jour., 1892, 126, 494.

⁹ Tidy, Lancet, 1868, i, 158.

¹⁰ Dragendorff, Ermittlung von Giften, Göttingen, 1895, 356.

is of uncertain strength and is no longer official; a few deaths have been reported from it.

The **fatal dose** of elaterium is placed at 7 or 8 grains (0.455 or 0.52 gm.), although an ill and feeble lady of seventy seems to have died from the purging caused by $\frac{2}{5}$ grain (0.026 gm.).¹

Detection.—The postmortem isolation of elaterin is not attended with certainty. The material under examination is extracted with hot alcohol, and the residue obtained after evaporation of the alcohol is boiled out with water, dried thoroughly, and extracted with ligroin, by which the poison is dissolved. Elaterin yields a carmin-red color on treatment with concentrated sulphuric acid that contains a trace of carbolic acid.

Podophyllum (U. S. P.) is the dried rhizome and roots of *Podophyllum peltatum* (May-apple, a common North American plant, also called mandrake); it is usually used in the form of the resin of podophyllum (U. S. P.), often called podophyllin, the active principle of which is podophyllotoxin.² Podophyllum is very irritating locally, and workmen who powder the roots or the resin may suffer severely from conjunctivitis.³ Added to blood it causes the formation of methemoglobin. The action of podophyllum when taken in medicinal doses is slow (twelve to twenty-four hours), but that of larger doses begins more promptly. In a fatal case⁴ the course was as follows: A woman took about 5 grains (0.32 gm.) of the resinoid podophyllin, instead of mandrake. Vomiting and purging began shortly after the drug was taken and continued for several hours. The extremities were cold; cold perspiration stood on the face; pulse 60, weak and thready; respirations sighing, and patient spoke with difficulty. The patient's condition rapidly improved and she got up, but was soon compelled to lie down again. The primary symptoms of depression returned, her mind showed aberration, but there was no purging or vomiting. Twenty-four hours after the poison was taken the patient was comatose. The urine was "smoky" and contained albumin and blood-cells. Patient died in a condition of coma about thirty-one hours after the drug was taken. The woman's husband took a similar dose and showed the same primary symptoms; these were followed by a depressed condition for two or three weeks and finally recovery. From these and similar cases the **fatal dose** may be placed at from 5 to 10 grains (0.32–0.65 gm.), although recovery followed the latter dose when administered to a strong woman,⁵ and a child twenty-two months old recovered from 4 grains (0.26 gm.).

Poisoning has been attributed to the eating of the fruit of the May-apple.⁶

Detection.—Both podophyllum and podophyllotoxin may be re-

¹ Craig, Amer. Jour. Pharm., 1868, 40, 373.

² Podwyssotzki, Arch. f. exp. Path. u. Pharm., 1881, 13, 29; Kürsten, Amer. Jour. Pharm., 1891, 63, 485.

³ Webster, Med. Rec., 1877, 12, 257.

⁴ Dudley, Med. Rec., 1890, 37, 409.

⁵ Prentiss, Phila. Med. Times, 1882, 12, 520.

⁶ Reynolds, Med. Rec., 1884, 26, 345.

moved from an acid aqueous fluid, as in an examination for alkaloids, by shaking with chloroform. Both substances are colored dark yellowish green by Mandelin's reagent.

Gamboge (Cambogia, U. S. P.) is a gum resin obtained from *Garcinia hanburii*. It has occasionally caused death from its use as a purgative and as an abortifacient; about 1 dram (3.9 gm.) has proved fatal. Gamboge is used as a pigment, and children are said to have been poisoned by moistening their lips with brushes that had been used in the pigment.

Detection.—There are no reliable tests for the detection of gamboge.

The **treatment** of cases of poisoning by the above purgatives is essentially the same as that mentioned under croton oil; demulcent drinks and opiates should be administered and great care should be taken with the diet, which should be as non-irritant as possible. Cardiac and respiratory stimulants may be necessary in conditions of collapse.

The only **postmortem appearance** commonly found is intense congestion of the alimentary tract with ecchymoses and bloody sero-fibrinous exudates with adhesions; sometimes there is ulceration of the entire gastro-intestinal canal. The peritoneum, liver, spleen, kidneys, and bladder have also been found congested.

IVY AND SUMAC POISONING

The plants responsible for the greatest number of cases of poisoning in the United States are members of a number of species belonging to the Rhus or Sumac family. The plants¹ involved vary much in appearance and include the vines and shrubs known as poison ivy (*Rhus radicans* or *toxicodendron*) and poison oak (*R. diversiloba*, etc.) and the poison sumac shrub or tree (*R. vernix*), but the effects produced by all seem to be identical. The active principle or principles are not fully known; Pfaff² attributed the action of *R. toxicodendron* and *R. venenata* to a non-volatile, oily principle which he called toxicodendrol; McNair,³ working with poison oak, obtained an oily poisonous liquid ("lobinol") which seems to be, or to contain, a polyhydric phenol.

The poisonous principle, which is insoluble in water but soluble in alcohol, occurs in all parts of the plant except the pollen, and is extremely potent; Pfaff found that 0.001 milligram ($\frac{1}{80000}$ gr.) of toxicodendrol would produce distinct effects when applied to the skin of some persons.

Poisoning usually results from direct contact with the plant, although this is not necessary; contact with articles of clothing, etc., or with individuals and perhaps animals who have come into contact with the plant is sufficient. The poison, although non-volatile, may be carried in the smoke from burning plants. Claims for damages on

¹ Sweet and Grant, Public Health Rep., 1920, 35, 443; McAttee, Med. Rec., 1920, 97, 771.

² Pfaff, Jour. Exp. Med., 1897, 2, 181.

³ McNair, Jour. Amer. Chem. Soc., 1921, 43, 159.

account of rhus poisoning have been made against owners of cemeteries, railroads, botanic gardens, etc.¹

The most common form of poisoning² is a severe inflammation and vesicular eruption of the skin. There are violent itching, redness, swelling, vesication, and, finally, desquamation. If the poison reaches the face, the swelling may be so great as almost entirely to obliterate the features; the patient may be unable to open the eyes for several days. The period at which the first symptoms appear after exposure varies greatly; they usually begin within four or five days, but may appear in less than a day or be delayed for a week or even longer. The latent period is shorter on the parts of the body where the skin is the thinnest, such as the face and scrotum. The lesions of herpes zoster have been mistaken for those of ivy poisoning.

Treatment.³—Numerous methods of treating rhus poisoning have been employed. In the early stages thorough washing with hot water and soap, or with alcohol, will usually prevent the further development of the poisoning. Washing the part affected with hydrogen peroxid or a hot alkaline 2 per cent. solution of potassium permanganate has been highly recommended. A strong solution of magnesium sulphate relieves the itching. Ointments should not be used in the acute stage as they tend to spread the toxic agent; in the late stages they may be useful in protecting the inflamed parts. Tinctures of rhus have been given internally; also intramuscularly for the immunization or "desensitization" or relief of individuals exposed to or suffering from ivy poisoning; favorable results have been reported.⁴

A few cases of poisoning, with at least 1 death,⁵ have resulted from the taking of rhus internally in order to secure immunity from the poison.⁶ A case⁷ is also reported in which an infusion of the root was



FIG. 68.—Poison ivy (*Rhus radicans*): a, Spray showing aerial rootlets and leaves; b, fruit.

¹ For a discussion of such cases see Rost and Gilg, Ber. d. Deut. Pharm. Ges., 1912, 22, 296; Rost, Med. Klin., 1914, 10, 101, 155, 198.

² McNair, Arch. Dermat. and Syph., 1912, 3, 383.

³ Ibid., 1921, 4, 62, 217.

⁴ Schamberg, Jour. Amer. Med. Assoc., 1919, 73, 1213; Strickler, Ibid., 1921, 77, 910.

⁵ Alumbaugh, Med. World, 1903, 21, 176.

⁶ McNair, Loc. cit.

⁷ Stokes, Med. and Surg. Reporter, 1867, 17, 373.

taken instead of sassafras tea; there was a rash resembling that of measles, with intolerable itching, suffusion of the eyes, and pain in the throat and stomach.

Moorman¹ reported a case of poisoning of children supposed to have resulted from the eating of berries of poison ivy; there were symptoms of local irritation and also evidences of effects upon the nervous system, as shown by drowsiness, stupor, and mild delirium; poisons other than that producing dermatitis may be involved (McNair). In experiments upon rabbits it was found that the internal administration of toxicodendrol

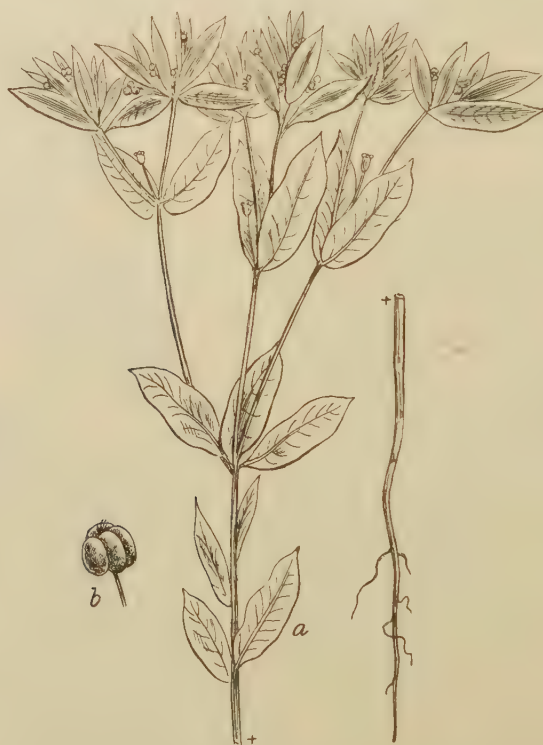


FIG. 69.—Snow on the mountain (*Euphorbia marginata*): a, Whole plant; b, seed capsule.

and lobinol caused albuminuria and nephritis,² and albuminuria is not uncommon in cases of severe poisoning in man (McNair); perhaps the few deaths attributed to poison ivy were due to this action upon the kidneys.

Detection.—To an alcoholic infusion of the material under examination is added an alcoholic solution of lead acetate, and the precipitated lead compound of toxicodendrol is suspended in water and decomposed with ammonium sulphid. After filtering off the lead

¹ Moorman, Amer. Jour. Med. Sci., 1866, 51, 560.

² Pfaff, Loc. cit.; McNair, Jour. Infect. Dis., 1916, 19, 419.

sulphid the active principle is shaken out with ether.¹ As there are no chemical tests known by which toxicodendron may be identified, the residue obtained after evaporating the ether should be dissolved in olive oil and applied to the skin. The characteristic eruption thus produced may serve, under the most favorable conditions, for the detection of $\frac{1}{1000000}$ gram ($\frac{1}{84000}$ gr.) of the poison.²

A number of other plants, either native to the United States or introduced, are known to produce skin eruptions more or less similar to those caused by rhus³; among these may be mentioned various varieties

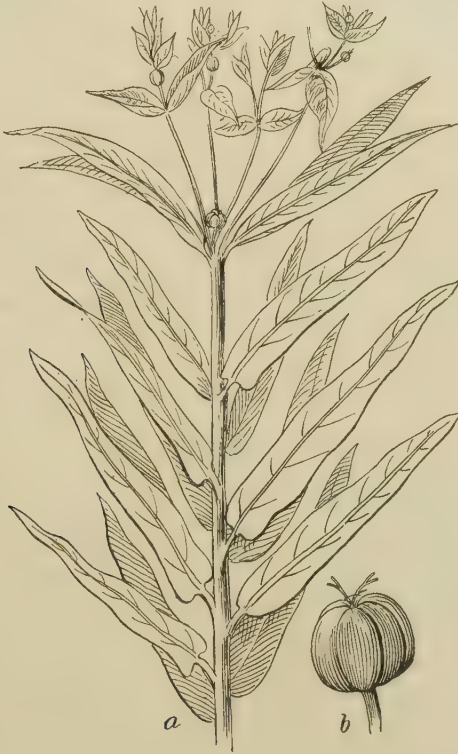


FIG. 70.—Caper spurge (*Euphorbia lathyris*): a, Upper half of plant; b, seed capsule.

of buttercups and crowfoot (Ranunculi), various species of Euphorbia, especially *Euphorbia corollata*,⁴ which was formerly official, and *E. marginata*⁵ or "snow on the mountains" (Fig. 69), and *E. lathyris* (Fig. 70), *Primula obconica*⁶ or primrose, rue (*Ruta graveolens*), Daphne

¹ Pfaff, Jour. Exper. Med., 1897, ii, 187.

² Pfaff, Ibid., ii, 192.

³ See White, Dermatitis venenata, 1887; Sequeira, Diseases of the Skin, 1919.

⁴ See Olive, Bull. Torrey Bot. Club., 1895, 22, 393.

⁵ See Jackson, Med. Rec., 1897, 51, 636; Schenk, Bot. Gaz., 1890, 15, 277.

Poisoning also results from the eating of honey derived from the flowers of *E. marginata*; the chief symptoms are vomiting and purging.

⁶ See Förster, Jour. Amer. Med. Assoc., 1910, 55, 642; Zeisler, Ibid., 1912, 58, 2024; Simpson, Ibid., 1917, 69, 95; Dreyer, Münch. med. Woch., 1902, 49, 574. A large number of cases are cited in the last article.

mezereum, and arnica. Several cases of poisoning have also been reported from handling various species of cypripedium¹ (lady's-slipper, moccasin flower); the effects were similar to those caused by rhus.

The application of a saturated solution of magnesium sulphate is often efficacious in relieving the itching which is present after poisoning by these plants.

TANSY

Tansy, the leaves and tops of *Tanacetum vulgare* (formerly in the U. S. P. as *Tanacetum*), a common plant in the United States, contains a volatile oil in which thujon² is present. Tansy is used extensively by the laity as an abortifacient, usually without success, and a number of deaths have occurred from this practice; it is also used occasionally as an anthelmintic.

The **symptoms**³ are similar to those caused by other volatile oils (see Oil of Turpentine, Savin, etc.); convulsions are common.

It is impossible to state the **fatal dose**⁴ of tansy; 1 dram (3.7 c.c.) of the oil has caused death in an hour and a quarter; 15 grams caused death in less than two hours. Recovery has followed 2 fluidrams (7.4 c.c.),⁵ and $\frac{1}{3}$ ⁶ and, it is said, $\frac{1}{2}$ of an ounce (15 c.c.). Severe poisoning has resulted from $\frac{1}{2}$ fluidram (1.85 c.c.) and even from 15 to 20 drops. A patient died twenty-six hours after taking an infusion of perhaps $\frac{1}{2}$ ounce of the dry herb.⁷

Detection.—There are no reliable tests for detection of tansy.

OIL OF PENNYROYAL

There are two preparations known as oil of pennyroyal—*Oleum hedeomæ* (formerly in the U. S. P.), derived from the common American pennyroyal (*Hedeoma pulegiosdes*), and the English oil of pennyroyal, derived from *Mentha pulegium*. These contain pulegon, an oil causing, in addition to local effects and nephritis, fatty degeneration of the liver. They are used by the laity as emmenagogues; they have also a certain reputation as abortifacients,⁸ and a few deaths have resulted from the use of not only the oil, but the plant itself (pennyroyal pills). Thus a woman died after taking a tablespoonful of the oil,⁹ the symptoms being those of gastro-enteritis. Other symptoms have been

¹ See Chesnut, *Principal Poisonous Plants of the United States*, 1896, 19; also *Northwestern Lancet*, 1898, 18, 382; *Bull. Torrey Bot. Club*, 1875, 6, 115; Jessup, *Bot. Gaz.*, 1893, 18, 142.

² Thujon is also contained in the leaves and tops of *Thuja occidentalis* (*Arbor vitæ*; "white cedar"), a plant much used in Europe as an abortifacient; of 5 cases of poisoning collected by Lewin (*Fruchtabtreibung*, 1904, p. 281), 2 were fatal.

³ Belt, *Med. Rec.*, 1889, 34, 342; Jewett, *Boston Med. and Surg. Jour.*, 1880, 52, 237; Dalton, *Amer. Jour. Med. Sci.*, 1852, 23, 136.

⁴ Ely, *Amer. Jour. Med. Sci.*, 1852, 24, 279.

⁵ Bailey, *Therap. Gaz.*, 1885, 9, 342.

⁶ Link, *New York Med. Jour.*, 1885, 41, 365.

⁷ Gallagher, *Phila. Med. Times*, 1881, 11, 346.

⁸ See Napier, *Brit. Med. Jour.*, 1890, i, 661; Flynn, *Ibid.*, 1893, 2, 1270; Marshall, *Ibid.*, 1890, i, 542; Girling, *Ibid.*, 1887, i, 1214; Wingate, *Boston Med. and Surg. Jour.*, 1889, 120, 536.

⁹ Allen, *Lancet*, 1897, i, 1022.

collapse, unconsciousness, coma; also excitement, convulsions, and dilated pupils. Macht¹ reported a case of poisoning with pennyroyal pills in which there was marked fatty degeneration of the liver. Macht² found the oil of pennyroyal (and also the oils of savin, tansy, rue, thyme, turpentine, and apiol) to be without direct action on the uterus.

Detection.—There are no reliable tests for the detection of pennyroyal.

NUTMEG

Nutmeg (*Myristica*, U. S. P.) is often used as an emmenagogue and (unsuccessfully) as an abortifacient; several cases of poisoning³ are reported from this use and also from its use as a flavor, or when eaten by children or from its use in domestic medicine.⁴ The symptoms are mainly narcotic, but there may be excitement and motor stimulation with choreiform movements; a flushing of the face, staggering gait, drowsiness, stupor, which may last four to thirty hours; delirium; sometimes burning pain in the stomach; sometimes collapse with small thready pulse; dilated, sometimes contracted, pupils.

Two nutmegs eaten by a boy of eight caused death in twenty hours.⁵ The narcotic effect is produced by "myristicin," the high-boiling portion of the volatile oil.

OIL OF CHENOPODIUM

Oil of American wormseed, *Oleum chenopodii* (U. S. P.), a volatile oil distilled from *Chenopodium ambrosioides anthelminticum*, which is used extensively as an anthelmintic, especially against round- and hookworms, has caused a number of cases of poisoning⁶ with several deaths. The toxicity is attributed, at least in part, to the presence of ascaridol, which is believed to be an unstable organic peroxid.⁷

Oil of chenopodium causes in animals gastro-intestinal irritation⁸ and symptoms of depression of the higher nerve centers, and then convulsions.⁹

In man the symptoms have been dizziness, nausea, abdominal pain,

¹ Macht, Jour. Amer. Med. Assoc., 1913, 61, 105.

² Macht, Jour. Pharmacol. and Exp. Ther., 1913, 4, 547.

³ Wallace, Contributions to Medical Research, ded. to V. C. Vaughan, p. 351, 1903 (collection of 25 cases); Cushny, Proc. Roy. Soc. of Med., 1908, 1, Ther. and Pharm., 39; Gibbins, Brit. Med. Jour., 1909, i, 1005; Mendelsohn, Deut. med. Woch., 1907, 33, 2001; Reckie, Jour. Amer. Med. Assoc., 1909, 52, 62; Lind, West Va., Med. Jour., 1910, 5, 90; Beck, Münch. med. Woch., 1914, 61, 878.

⁴ Wilkinson, Brit. Med. Jour., 1906, i, 539.

⁵ Dodge, New York Med. Rec., 1887, 32, 624.

⁶ Levy, Jour. Amer. Med. Assoc., 1914, 63, 1946; Roth, Southern Medical Jour., 1918, 11, 733; Oppikofer, Correspondenzbl. f. Schw. Aerzte, 1919, 49, 161; Rhyiner, Ibid., 360; Preuschoff, Zeits. f. exp. Path. u. Ther., 1920, 21, 425 (summary of 24 cases); Darling, Barber, and Haeker, Jour. Amer. Med. Assoc., 1918, 70, 499; Evers, Deut. med. Woch., 1921, 47, 857.

⁷ Nelson, Jour. Amer. Chem. Soc., 1911, 33, 1404; 1913, 35, 84. See also de Almeida, Brazil Med., 1922, 1, 324; Leite, Ibid., 340.

⁸ Hall and Hamilton, Jour. Pharm. and Exp. Therap., 1918, 11, 89.

⁹ Salant and Nelson, Amer. Jour. Physiol., 1915, 36, 440.

cramps, vomiting, headache, rapid and irregular pulse, hallucinations, drowsiness, coma, clonic convulsions, and death from arrest of the respiration. The symptoms may develop suddenly after two or more courses of treatment; there is a distinct tendency to a cumulative action.

Deafness is a frequent sequel to chenopodium poisoning; it has varied from very mild to complete loss of hearing and has persisted for at least two years. Staggering, extreme vertigo, and ataxia have been reported; also aphasia and jaundice and, rarely, disturbances of vision.

The **fatal dose** is not known. Many of the fatal cases have been in children and have frequently followed the administration of a number of small doses: thus children of five and seven years have died from three daily doses of 0.5 gm. of the oil repeated for two or three days. Death has occurred within a few hours, but more frequently, apparently, not for from one to four days. Recovery, if it occurs, is slow.

There are no characteristic postmortem findings.

PICROTOXIN

Picrotoxin is obtained from *Cocculus indicus*, which is the dried fruit of *Anamirta paniculata*, a climbing shrub of the East Indies; the fruit is also known as fish-berries, grains of paradise, and Levant nuts. The powdered berries have long been used as fish and bird poisons; they have also been used to a limited extent in medicine, chiefly as parasiticides and as a household remedy for vermin. At one time they were frequently added to beer to give it a stronger flavor.

Most cases of poisoning from picrotoxin have been due to accident; in all the reported cases the berries or preparations of them have been used. The berries have been mistaken for wild cherries,¹ for cubebs, or for pepper, with fatal results. Death has resulted from the drinking of tinctures intended as remedies for vermin.² In a case cited by Taylor several men were poisoned by rum that had been impregnated with them. They have been added to alcoholic liquors to make "knock-out" drops.

Properties.—*Cocculus indicus* contains about 1 per cent. of picrotoxin, which is a neutral body acting, however, as a weak acid toward strong bases, and having the formula $C_{30}H_{34}O_{13}$. Picrotoxin is slightly soluble in cold, more soluble in hot, water, and readily soluble in alcohol, ether, and chloroform. It forms colorless crystals melting at from 192° to 200° C. (377.6°–392° F.); it is odorless, but is intensely bitter.

Picrotoxin is a powerful stimulant to parts of the central nervous system and causes powerful convulsions in which the clonic form predominates; there is usually loss of consciousness; in many cases there is also a stimulation of the spinal cord, for tonic convulsions alternating with the clonic have been described, and there is also increased reflex excitability.

Symptoms.—A few minutes after the poison is swallowed there is

¹ Shaw, Med. News, 1891, 59, 38.

² Sozinsky, Ibid., 1883, 43, 485; Swift, New York Med. Jour., 1897, 66, 664.

felt a burning pain in the esophagus and stomach, followed shortly by salivation, nausea, vomiting, and diarrhea. There are weakness, confusion, dizziness, headache, drowsiness, cold, profuse perspiration, and unconsciousness; the face is pale, the pupils may be contracted or dilated, or these conditions alternate; the respiration is at first rapid and labored; later it is slow. Convulsions usually begin early (in twenty minutes,¹ for example); in Sozinskey's case they were as follows²: powerful general convulsions followed each other every five minutes or so, each lasting about two minutes. Between the convulsions there was perfect relaxation; hence they were very pronouncedly clonic. There was considerable opisthotonos. Each convulsion began with twitching of the muscles about the left corner of the mouth. As each attack came on there was more or less of an outcry, as in epilepsy, and some frothing was observable at the mouth.³ In Thompson's case the pupils are described as being contracted during a convulsion and dilated between them; by touching the eyelid a spasm could be caused at pleasure, indicating an increased reflex excitability, as in strychnin poisoning. Consciousness is lost during the convulsions. The flexors are the muscles usually involved; sometimes, however, the jaws are firmly closed, as in strychnin poisoning. The pulse is sometimes weak; sometimes it is but little affected. Death results from respiratory failure.

Fatal Dose and Period.—No cases of death from pure picrotoxin are reported; $\frac{1}{3}$ grain (0.022 gm.) has caused unpleasant symptoms, and from experiments on animals it is thought that 2 or 3 grains (0.13 or 0.195 gm.) would be a dangerous dose for man. Death is said to have resulted, however, from 36 grains (2.4 gm.) of the powdered berries; this would equal but about $\frac{1}{3}$ grain (0.022 gm.) of picrotoxin.

In several cases death occurred in thirty minutes. In the case reported by Swift death occurred in forty-five minutes; in a case reported by Rosenkrans,⁴ within an hour; in Sozinskey's case it occurred in three hours. In Thompson's case, in which the drug was absorbed from the skin, death occurred in about six hours. In a case cited by Taylor death occurred from gastro-enteritis nineteen days after the poison was taken; in a similar case described by Mitchell⁵ death occurred in twelve days.

Treatment.—The stomach should be evacuated by the stomach-tube or by emetics. Chloroform may be given during the convulsions. It is probable that moderate doses of chloral hydrate⁶ would be of value, but this drug must be used with caution, for the picrotoxin kills in the same way as chloral does—viz., by paralyzing the respiratory center. Hot mustard baths and other stimulants have been used in the late stages.

Postmortem Appearances.—In animals killed by picrotoxin

¹ See Wharton and Stillé, *Med. Jurisp.*, 1873, ii, 596.

² See also Haynes, *Phila. Med. Times*, 1884, xiv, 748.

³ Sozinskey, *Loc. cit.*

⁴ *Northwestern Med. and Surg. Jour.*, 1849, i, 295.

⁵ Mitchell, *Therapeutics*, 1850, 313.

⁶ See Browne, *Brit. Med. Jour.*, 1875, i, 540.

there may be hyperemia and edema of the lungs and hyperemia of the meninges, and occasionally redness of the mucous membrane of the esophagus and stomach. No characteristic lesions have been found in man.¹

Isolation.—Picrotoxin may be extracted from an acid aqueous fluid with chloroform or amyl alcohol, but the material obtained from animal substances in this manner is usually so impure that it will not respond to the tests, and various methods of subsequent purification have been suggested.² Palm³ claims that all these modifications are defective, and gives the following process:

The material under examination is evaporated to dryness and extracted with acidified water. The picrotoxin is removed from the acid solution with ether, the ether evaporated, and the residue taken up again in water and decolorized with animal charcoal. Neutral lead acetate is now added as long as a precipitate is formed, and after filtration the liquid is agitated with freshly precipitated lead hydroxid, which forms an insoluble compound with picrotoxin. The lead compound may be suspended in water, decomposed with sulphuretted hydrogen, and the picrotoxin extracted from the aqueous fluid with ether.

Tests.—1. A minute quantity of the suspected substance is evaporated to dryness with concentrated nitric acid, and the residue moistened with concentrated sulphuric acid. On the addition of an excess of potassium hydroxid the presence of $\frac{1}{10000}$ gram ($\frac{1}{650}$ gr.) of picrotoxin will be shown by the appearance of a brick-red color.⁴

2. Picrotoxin dissolves in concentrated sulphuric acid with a golden-yellow color that, upon the addition of a trace of potassium bichromate, changes to violet and then to brown. This test may be applied directly to the lead compound obtained in Palm's process.

3. Picrotoxin boiled with vanillin-hydrochloric acid gives a green color after a few minutes.

4. On heating picrotoxin in a subliming cell a sublimate in the form of drops appears at about 215° C. (419° F.). With HCl these drops give crystals. O. Tunmann⁵ prefers using 5 per cent. ferric chlorid solution. If the sublimate is treated with 1 drop of this solution and heated under a cover-glass until bubbles appear, typical pentagonal tablets are observed on cooling.

5. A small particle of picrotoxin treated with 2 drops of an alcoholic (absolute) solution of benzaldehyd (1 : 1) and then with 1 drop of concentrated sulphuric acid becomes red. If the liquid is agitated it obtains a reddish-violet color (Melzer).

CICUTA (WATER HEMLOCK)

Several species of *cicuta* are very poisonous; the one most carefully studied is *Cicuta virosa*, a common European plant which has long

¹ Compare Swift, loc. cit.

² Chlopinsky, Jahresber. der Chemie, 1884, 1644.

³ Zeitschr. f. anal. Chem., 1883, xxii, 274; 1885, xxiv, 556; 1888, xxvii, 99.

⁴ Langley, Ibid., 1863, ii, 404; Chlopinsky, Loc. cit.

⁵ Tunmann, O., Apoth. Zeit., 1917.

been known to be very toxic and which has been used for suicide and also for homicide.¹ In this country *C. maculata*, which is very similar to, if indeed it is not identical with, *C. virosa*, is the most important. Other plants belonging to this genus are *C. vagans*, or Oregon water hemlock, which is found in the far Northwest; *C. bulbifera*, which is found in the Great Lake States and also in the East, and *C. occidentalis*, found in the Rocky Mountains.

Boehm² and Pohl³ isolated from *C. virosa* a bitter, resinous, very poisonous principle, named by the former cicutoxin; Jacobson⁴ has



FIG. 71.—Water hemlock (*Cicuta maculata*). Showing section of spindle-shaped root and lower stem, the leaves, flowers, and fruit, also fruit and cross-section of seed.

isolated from *C. vagans* the same or a similar body of the formula $C_{19}H_{26}O_3$, which he finds to be a derivative of pyrone. The physiologic action of cicutoxin is very similar to that of picrotoxin.

C. maculata (American water hemlock; wild hemlock; spotted hemlock; spotted parsley; snake-weed; beaver poison; musquash root; muskrat weed; cowbane; children's bane; death of man). According

¹ Přibram, Arch. f. Krim. Anthropol. u. Kriminalistik, 1900, iv, 166.

² Boehm, Arch. f. exp. Path. u. Pharm., 1876, v, 284.

³ Pohl, Ibid., 1894, xxxiv, 265.

⁴ Jacobson, Jour. Amer. Chem. Soc., 1915, xxxvii, 916.

to Chesnut¹ and Marsh, Clawson, and Marsh this is one of the most poisonous plants native to the United States. All parts of the plant are poisonous, but the underground parts are especially dangerous; these have been mistaken, with fatal results, for horseradish, parsnips, artichokes, sweet cicely, angelica, and other edible roots. Most of the cases have occurred in children. The plant is also very destructive to cattle.

The **symptoms**,² which may begin within a few minutes after the plant is eaten, are dizziness, pain in the abdomen, salivation, violent,



FIG. 72.—Oregon water hemlock (*Cicuta vagans*): a, Plant with leaves; b, root-stock and horizontal roots; c, section of root-stock; d, flowering spray.

sometimes bloody, vomiting, cold skin, profuse perspiration, slow, weak pulse, unconsciousness, and frequent violent epileptiform convulsions, as in picrotoxin poisoning.³ The pupils are usually widely dilated and do not react to light; the jaw may be firmly closed.⁴

¹ Chesnut, Principal Poisonous Plants of the United States, U. S. Dept. of Agriculture, 1896, 40. Cf. Marsh, Clawson and Marsh, Bulletin No. 69, U. S. Dept. of Agriculture (Bur. Plant Ind.), 1914.

² Compare Egdahl, Arch. Int. Med., 1911, vii, 348.

³ In a non-fatal case reported by Folk (Trans. So. Car. Med. Assoc., 1882, 69) there were apparently no symptoms for several hours.

⁴ Schuette, Botanical Gaz., 1885, x, 386.

The **fatal dose** is not known; Chesnut says that a piece of the root of *C. vagans* the size of a marble is considered dangerous to man. A piece of the root of *C. maculata* the size of a filbert caused no unpleasant symptoms.¹ Of 5 persons poisoned by *C. occidentalis* in Montana in 1901, 4 died.

Death may occur in an hour.² In a case cited by Maisch³ 3 children died within three hours after eating some of the root of *C. maculata*; in other cases life has been somewhat prolonged.

The **treatment** should be similar to that for picrotoxin poisoning, viz., evacuation of the stomach, the administration of the bromids, the cautious use of chloral hydrate or of chloroform, and, in the later stages, of stimulants (rubbing the skin with flannel soaked in hot brandy, mustard baths, etc.).

No characteristic **postmortem changes** have been described.

Detection.—In the present state of our knowledge concerning the active principle of *C. maculata* the toxicologist would have to rely largely upon the microscopic appearances of any remnants of the plant found in the vomited matter. The coniin-like odor is also of aid. European writers recommend that in cases of poisoning by *C. virosa* the contents of the stomach and intestines be extracted with ether and the residue be used for experiments upon animals. Cicutoxin, for which no chemical tests are known,⁴ produces effects upon frogs almost identical with those caused by picrotoxin: among these effects are convulsions of medullary origin—i. e., the convulsions disappear when the cord is separated from the medulla, but persist when the latter is separated from the forebrain. Such vital tests should be done only by an experienced pharmacologist.

LAUREL⁵

Many members of the heath family (Ericaceæ) are poisonous from the presence of andromedotoxin. The best known of these plants in the United States are *Kalmia latifolia* ("broad-leaf laurel," "mountain laurel," "mountain ivy," etc.), in which andromedotoxin was found by Plugge,⁶ and *Kalmia angustifolia* ("narrow-leaf laurel," "lambkill," "dwarf laurel," etc.), in which the same principle was found by Lasché.⁷ The former is found chiefly on rocky hillsides and mountain slopes up to from 3000 to 4000 feet from Connecticut to Eastern Ohio and along the Alleghanies to Georgia; the latter is abundant at low altitudes from Maine to New Jersey, less abundant throughout the Great Lakes region, and south to Tennessee and South Carolina.

Little is known about andromedotoxin beyond the fact that it is

¹ Crozier, Botanical Gaz., 1889, xiv, 18.

² Smith, Ibid., 1888, xiii, 128; Crozier, Ibid., 1889, xiv, 18.

³ Maisch, Amer. Jour. Pharm., 1891, 63, 322.

⁴ Dragendorff, Ermittlung von Giften, 1895, 297.

⁵ See Chesnut, Principal Poisonous Plants of the United States, 1896, 44.

⁶ Arch. d. Pharm., 1889, 227, 164 (cited in the Amer. Jour. Pharm., 1889, lxi, 361).

⁷ Pharm. Rundschau, 1889, vii, 208 (cited by Plugge, Arch. d. Pharm., 1891, cccxix, 553).

free of nitrogen and that it is not a glucosid; the formula is $C_{31}H_{51}O_{10}$. It is contained in *Kalmia latifolia* to the extent of about 0.05 per cent. It is very poisonous, 1 to 2 milligrams ($\frac{1}{60}$ to $\frac{1}{30}$ of a grain) per kilogram of animal being fatal to rabbits. The physiologic action of andromedotoxin is, in general, similar to that of aconitin.

But a few cases of laurel-poisoning among human beings are reported. In some cases the poisoning resulted directly from eating the plant or from decoctions used in domestic medicine. The Indians are said to have sometimes committed suicide by drinking such decoctions.



FIG. 73.—Broad-leaf laurel (*Kalmia latifolia*): a, Flowering spray; b, vertical section of flower, showing peculiar attachment of stamens; c, fruiting capsules.

In other cases honey¹ derived from the nectar of the flowers has been held responsible, or the flesh of birds² that had eaten the leaves; accurate observations on this subject are lacking. It is said that a decoction of laurel leaves is sometimes added to cheap whisky in order to increase its intoxicating effects. Many cattle and sheep are poisoned annually by eating the leaves.

¹ Coleman is said to have described in the New Jersey Medical Reporter for 1852, p. 46, the poisoning of 14 persons from eating wild honey supposed to have been collected from the flowers of *Kalmia angustifolia*: one patient died. The poisonous honey mentioned by Xenophon in the *Anabasis* was probably derived from *Rhododendron ponticum*, which contains andromedotoxin.

² United States Dispensatory, 16th ed., 1888, 1834; cf. Chesnut, Science, 1902, 15, 1024.

Isolation and Detection.—Andromedotoxin¹ may be obtained in nearly pure form by dissolving the residue left after evaporation of an alcoholic extract in water, shaking this solution with ether, in which it is but slightly soluble, and then with chloroform. The andromedotoxin is extracted by the chloroform; by evaporating the chloroform, dissolving the residue in alcohol, and allowing the latter to evaporate slowly the andromedotoxin may be obtained in pure form. Andromedotoxin is more soluble in cold than in hot water; it is not precipitated by the alkaloidal reagents, and on heating with sulphuric and hydrochloric acids, a red color is produced.

LOCUST

A few cases of poisoning are reported from the eating of parts of the common locust (*Robinia pseudacacia*); in some cases the leaves, in others the roots, but most frequently the bark, was the part responsible. Emery² described the poisoning of 32 boys from chewing the inner bark of the tree, which they had obtained from a yard where fence-posts had been stripped; the symptoms were vomiting, flushed face, dryness of the throat and mouth, and dilated pupils. In the more severe cases there were epigastric pains, extremely feeble, intermittent heart action, and stupor, from which the patients could be aroused with difficulty. The severity of the symptoms seemed to be somewhat independent of the quality of bark chewed.

In a case cited by Lewin³ the symptoms were similar, but there were also convulsive movements, as in belladonna poisoning, livid lips, and sunken eyes.

Cases of poisoning from eating locust leaves are reported from China⁴; a day or two after the leaves are eaten there are some fever and edema, first of the mouth, later of the entire skin. The edema of the lids is especially marked. In about a week there is desquamation of the entire skin, as in scarlet fever.

The toxicity of the leaves is said to be diminished by cooking.

According to the investigation of Power and Cambier,⁵ and of Power⁶ the toxic principle of the bark is a protein called robin by Ehrlich. Ehrlich⁷ found that this substance injected into animals caused an exudate in the serous cavities, ulcers in the gastric mucosa, and acute nephritis; it leads to the formation of an antibody similar to antiricin.

A glucosid, "robinin," has been obtained from the flowers.

Detection.—There is no reliable test for detection of locust.

¹ See Archangelsky, Arch. f. exper. Path. u. Pharm., 1901, xlv; 318; also Hardikar, Jour. Pharm. and Exp. Therap., 1922, 20, 17.

² Emery, New York Med. Jour., 1887, xlv, 92; see also Geltich, Phila. Med. Times, 1880, x, 387.

³ Lewin, Lehrb. der Toxicol., 1897, 283; the case was described in the Ann. de Thérap., 1860, 64.

⁴ Coltman, Med. and Surg. Reporter, 1889, 61, 236.

⁵ Power and Cambier, Pharm. Rundschau, 1890, 8, 29.

⁶ Power, Pharm. Jour., 1901, 67, 258; Amer. Jour. Pharm., 1913, 85, 339.

⁷ Ehrlich, Deut. med. Woch., 1891, 17, 1218; Klin. Jahrb., 1897, 6, 299.

INDUSTRIAL TOXICOLOGY

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Introduction.—The list of poisons which may be classed as industrial is not large and the members belong chiefly to the heavy metals, arsenic, antimony, and phosphorus, the heavy acids, various sulphur compounds and cyan compounds, carbon monoxid, and the organic compounds belonging to the aromatic and the fatty series. For the most part these poisons are encountered also outside of industry, but there are a few industrial poisons which are not used medicinally nor for any non-industrial purpose and which are, therefore, purely industrial poisons. These are brass, manganese, white phosphorus, carbon disulphid, several members of the aromatic series, especially nitro compounds such as dinitrobenzene and trinitrotoluene, amido compounds such as anilin, and several of the fatty group such as tetrachloroethane, amyl acetate, methyl bromid, and dimethyl sulphate. In this brief review of the subject it will be impossible to do more than point out the special features of industrial as compared with general toxicology and to give the salient facts regarding the more important industrial poisons, the trades in which these are encountered, and the actual amount of poisoning that is known to have occurred from their use in American industry.

Poisons usually find their entrance into the human body through the mouth, less often through the breathing of poisonous gases, and even more rarely by way of the skin. In industry there are mechanical difficulties in the way of mouth ingestion for it can occur only if the workman puts his poison-smeared fingers in his mouth or handles his food or chewing tobacco in such a way as to soil them with poisonous dust. This mode of entrance is not unknown in industry, but it gives rise to only a fairly slow form of poisoning and probably only of moderate severity. By far the most important mode of entrance is through the inspired air. This is true not only of the poisonous gases, but also of poisonous dusts and fumes, for fumes are really extremely fine suspensions of dust. Whether or not the dust that is inspired suffers absorption chiefly through the lung capillaries or through the gastro-intestinal tract is an unsettled question. Saito's¹ experiments in K. B. Lehmann's laboratory showed that the great bulk of the dust that is breathed in is caught in the mucus of the nose and pharynx and swallowed, but it is possible that the relatively small portion which reaches the lungs is more important because it can pass at once into the capillaries, while

¹ K. B. Lehmann, Y. Saito, and H. Majama. Arch. f. Hyg., 1910, lxxv, 160.

that which is taken up from the intestinal tract must first go through the liver. However this may be, it is necessary to emphasize the fact that there is incomparably more danger of industrial poisoning from dust and fumes in the factory than from lack of personal cleanliness on the part of the workman who does not eat more than three times a day, but is obliged to breathe throughout his eight- or ten-hour working day.

Absorption through the skin comes next in importance. This is the path taken by the majority of the organic poisons, even when these are volatile and also enter with the inspired air. In many instances it is impossible to say whether fumes or skin contact is chiefly responsible, but with regard to certain aromatic compounds, such as anilin, dinitrobenzene, and trinitrotoluene, our experience during the war showed that fumes were not nearly so great a danger as skin contact. In industrial mercurialism both modes of entrance are followed and the same is true of industrial methyl alcohol poisoning. Skin absorption is, so far as we know, negligible with regard to the lead compounds used in industry. The water-soluble salts, the acetate, and nitrate, are very little used. Here again the importance of factory conditions must be emphasized. No matter how cleanly a workman may be, he may not wash more than once in five hours and in the periods between his skin may be covered with poison. The conditions under which work is carried on have an influence on the occurrence of industrial poisoning. Heat undoubtedly increases the danger, especially of those poisons which enter through the skin, for heat flushes the surface vessels and increases sweating. During hot weather there is always a decided increase of sickness in coal-tar dye workers and in men who handle T. N. T. Long hours of work increase the dose of poison and shorten the period of elimination, whether or not we take it as proven that fatigue lowers the resistance of the body to poisons. Poor food, causing indigestion and constipation, interferes with the elimination of the poison, and A. J. Carlson¹ has shown that the drinking of milk between meals in order to insure the presence of protein in the stomach is a valuable prophylactic measure against lead-poisoning. It is needless to say that immature workers suffer more severely from exposure to the industrial poisons than do adults. This fact is recognized in European countries and embodied in protective legislation.

Industrial poisoning is typically chronic, exceptionally acute, although this is not so strikingly true in the United States where the protection of workers in the dangerous trades is still very incomplete. Workmen are exposed to much more massive doses of certain poisons in this country than they are in the older countries and we have, therefore, a larger proportion of acute lead, manganese, arsenic, benzene, wood alcohol poisoning than is true in the older countries. However, even here the instances of chronic poisoning, though less conspicuous, are more numerous and usually more serious than the acute.

The clinical picture of a case of industrial poisoning is very likely

¹ A. J. Carlson and A. Woelfel, *Jour. Amer. Med. Assoc.*, 1913, lxi, 181.

to be atypical because mixed poisoning is so frequent. For instance, in the smelting of lead, arsenical poisoning is almost always a possibility; in the smelting of zinc, both lead and arsenic may be present. Makers and users of varnish are exposed to a mixture of volatile solvents such as benzene, methyl alcohol, and amyl acetate. A fatal case of poisoning in a man who was making carbanilid in a rubber factory from anilin and carbon disulphid had a history which was not typical of either compound. Even if a workman is handling but one compound, he may be exposed to fumes or dusts from some process which is carried on in the same room. For instance, a man employed on a nitrator was found to be suffering not only from nitrogen oxid fumes, but even more seriously from dinitrobenzene fumes from the cooling pans near by. The diagnosis is often rendered difficult by the ignorance of the man as to the substance he is using. A group of painters in Cincinnati in 1912 complained of a very rapidly developing form of lead-poisoning from the use of quick drying paints, but these paints proved to contain no lead and the substance responsible for the trouble was the naphtha which had been substituted for linseed oil. The Illinois Commission on Occupational Disease in 1910 discovered 15 cases of lead-poisoning among commercial artists who, supposing that they were using harmless zinc white, had the habit of putting the brush in the mouth to bring it to a point. The cases were reported to the Commission as suffering from an unusual form of zinc-poisoning.

The following is a list of the industrial poisons which are known to be of importance in the United States: metallic lead, lead sulphid, litharge, red lead, basic sulphate, basic carbonate, chromate; arsenic trioxid, aceto-arsenite of copper, lead arsenate, hydrogen arsenid; metallic antimony, antimony sulphids; volatilized zinc oxid; metallic mercury, acid nitrate of mercury; manganese; white phosphorus; cadmium; hydrocyanic acid, potassium and sodium cyanid, calcium and sodium cyanimid; vanadium; selenium; nitric acid and its anhydrids; sulphuric acid and its anhydrids; hydrochloric acid and chlorin; hydrofluoric acid; potassium and sodium bichromate and hydrate; hydrogen sulphid; carbon disulphid; carbon monoxid; the petroleum distillates, especially the lighter, methyl alcohol, amyl alcohol, amyl acetate, dimethylketone, formaldehyd, dimethyl sulphate, methyl chlorid, tetrachlorethane, tetrachloromethane, and sulphuric ether; nitroglycerin; benzene and toluene and their nitro-, amido-, chlor-, and hydroxy- derivatives; phosgene or carbonyl chlorid; turpentine.

In the necessarily brief consideration that can be given here to the principle industrial poisons it seems best to describe only those features which are distinctive of poisoning as it is found in industry. The actual statistics will be drawn as much as possible from American sources and are offered not with any claim of completeness, but as merely suggestive.

Lead is not only the most important of the metallic poisons, but it is probably the most important toxic element used in industry, and there is almost as much literature on lead-poisoning as on all other in-

dustrial poisons put together. It is encountered in lead mining chiefly as the sulphid or galena, but in some of the Western mines where the ores lie nearer the surface oxidized ores are still mined. There is only slight danger of plumbism among miners of pure galena, although Carlson's¹ experiments showed that the lead of galena ore is soluble in human gastric juice in proportions running from 1.38 to 3.32 per cent. The United States is the largest lead-producing country in the world and in addition to smelting and refining the product of our own mines we also refine Mexican bullion. This industry is fraught with many dangers and the rate of lead-poisoning among the employees, which in 1913 was found to be 23 per cent.,² is probably still high. Dust is the great danger in the crushing and grinding mills, in the sampling mills (27 cases of plumbism in one mill in 1912 with a regular force of only 30 men), on the feed floor of the furnaces, and in the flue and bag house system. In this last department the work of cleaning out the sublimed oxids and sulphate is rightly regarded as the most dangerous work of all, and the incidence of plumbism at the regular annual or semi-annual cleaning may run from 50 to 80 per cent. The danger of fumes is encountered at the tapping-floor of furnaces, especially the blast furnace and the cupels, and the so-called Scotch hearths or open hearths, which are still used in three large American smelters. Severe and even fatal forms of lead-poisoning were found in 1913 in hospital records and in the records of physicians, including 41 cases of lead encephalopathy, 35 of palsy, and 16 deaths. The records of the individual plants differed very much, the lowest rate being 18 per cent. of plumbism per year and the highest 52.3 per cent. The rate in Great Britain for the same year was 1.8 per cent. Four German smelters had between 10 and 11 per cent., and the largest Bohemian smelter had 9 per cent.

Metallic lead is used in a vast number of industries, such as the making of wire, pipe, sheet, machine parts, plumbers' goods, storage battery plates, bullets and shrapnel, car and can seals, solder, babbitt, printers' type, and electrotype and stereotype plates. Solid lead freshly cast gives little trouble, but exposed to the air it becomes gradually covered with a layer of gray oxid which is easily detached and wiped off by the fingers or scattered as dust in the air. This oxidation takes place much more rapidly when lead is molten, and the finely divided oxid may be carried up with the waves of heat when the surface of the molten mass is stirred or skimmed. The general idea prevails in the lead industry that there can be no contamination of the air from molten lead under a temperature of 1000° C., when it begins to volatilize, but Roth³ was able to prove the presence of lead in the air above a kettle heated to 650° C., and Riemsdyk⁴ says that slight amounts begin to be given off after the melting-point of 326° C. has been reached. These tests were all made with molten lead at rest.

¹ A. J. Carlson and A. Woelfel, *Jour. Pharmacol. and Exper. Therap.*, 1913, v, 549.

² U. S. Bureau of Labor Statistics, *Bull.* 141, 1914.

³ O. Roth, *Beitr. z. path. Anat. u. allgem. Path.*, 1905, vii, Suppl. 184.

⁴ Riemsdyk, *Dommer's Hb. d. anorgan. Chemie.*

Earle Phelps¹ found that if the lead pot were agitated, as it is in actual lead work, contamination of the air might occur when the temperature of the pot was at 310° C. Such fumes are encountered not only by the makers of leaden objects, but by solderers and by lead burners who melt together two leaden surfaces by means of an oxyhydrogen flame. Both fumes and dust are encountered by lead temperers who drop machine parts, magnetos, piano wires, etc., into molten lead and take them out, and after cooling them rub off the adherent lead. These industries all have a rate of lead-poisoning which is unduly great, considering the comparatively slight danger connected with the making of leaden objects, for the temperature is never very high and the quantity of soluble lead present is almost always very small. Careful regulation of the work could practically eliminate all danger except for very susceptible men.

The printing trade deserves special mention among those using metallic lead. It is a notoriously unhealthful industry in all countries, but how large a part of the harm is to be attributed to the lead remains an unsettled question. The rate of plumbism among printers is never high. W. W. Palmer of Boston, and J. D. Ellis² of Chicago, found 9 per cent. of 200 printers examined by them to show evidence of chronic plumbism, but only 46.5 per cent. of the whole number were found to be free from noteworthy symptoms of ill-health although they did not present the typical picture of plumbism. Hahn's³ statistics from the German sickness insurance records show that there is a close connection between plumbism and tuberculosis in printers, the two rates falling together as hygienic conditions in the industry improve.

Another metallic lead trade—the plumbers'—becomes less dangerous all the time as less lead piping is used, but occasional cases of lead-poisoning are found among plumbers, as in Illinois in 1910, when 19 of the 560 cases of industrial plumbism found by the Occupational Disease Commission were in plumbers.

Of the lead compounds used in industry the most important are the basic carbonate, known as white lead, and the oxids, litharge, and red lead. The last two are not as toxic as the basic carbonate, but in actual use they seem to give rise to as much poisoning as does white lead, probably because they are lighter and fluffier, and therefore it is harder to prevent the escape of dust when the work requires that they be handled dry. White lead is made on a large scale by the Old Dutch Process and by a new quick process known as the Carter. In both of these the great danger is from dust, but the industry has undergone radical changes during recent years, machinery has taken the place of much of the hand work, and the sanitation and medical control of the great majority of these plants are excellent. The proportion of cases among the workmen has fallen very decidedly and periodical

¹ Earle Phelps, U. S. Bureau of Labor Statistics; *Hygiene of the Printer's Trade*, Bull. 209, 1917, 14.

² *Ibid.*, 93.

³ M. Hahn, *Die Gesundheitsverhältnisse im polygraphischen Gewerbe Deutschlands*. Bericht an die internationale Vereinigung für gesetzlichen Arbeiterschutz, 1908.

medical inspection of the men prevents the development of the serious forms of poisoning which ten years ago were deplorably common. White lead is the agent responsible for most of the lead-poisoning of painters, but red lead paint is still used on steel ships, in structural iron work, bridge building, etc., and the chipping off of old red lead paint has given rise to some cases of very severe poisoning. Painters also use the yellow chromate, although not nearly so much as formerly, for anilin yellows are cheaper. Lead chromate with potassium ferrocyanid forms chrome green, still used for painting window blinds and dyeing window shades.

The use of sulphate of lead, known as sublimed white lead, as a substitute for the basic carbonate, is increasing and is an advantage when the health of the men is considered, for the sulphate is distinctly less soluble in human gastric juice than is white lead.¹

The lead-poisoning of painters is, of course, notorious, and probably the severest forms of plumbism are seen in this industry because it is a skilled trade which a man does not readily abandon even when he knows that he is running a great risk of losing his health. It seems to be the one lead trade which does not show a diminution of plumbism in the last ten years in Germany or in Great Britain. We have no statistics in this country to show whether it is diminishing or not, but we have records of a few studies made of groups of working painters. Thus, Hayhurst² examined 100 working painters in Chicago in 1913 and found indications of chronic plumbism in 70, in 59 of whom the diagnosis seemed clear. In 1918 L. I. Harris³ of New York, examined 304 painters, 162 of whom, or 53 per cent., had symptoms of plumbism, and 75 gave a definite reaction for lead in the urine.⁴

The basic carbonate is used also in making glaze for pottery and tiles. The addition of lead to glaze makes it fusible at a lower temperature. Colors used in decoration are changed if fired at too great a heat and therefore decorated pottery and tiles must be covered with a glaze fairly rich in lead, while white ware and white tiles may contain little or none. In Great Britain, establishments using glazes with more than 5 per cent. soluble lead must use extraordinary measures of protection for their glaze workers. The dangerous processes in potteries and tile works are: mixing the glaze, dipping the ware in liquid glaze, "finishing" or "fettling," *i. e.*, scraping off the superfluous glaze, placing the glazed ware in saggars for the kilns, and applying lead color by means of a compressed air spray or by dusting it on with pledgets of cotton.

Red lead is used in some glazes, especially for tiles, in the making of storage batteries, as an ingredient of paint, and in the enamel for sanitary ware. Litharge is used for storage battery plates and in compounding rubber, glass, and some glazes. Of these industries, the

¹ A. J. Carlson, Jour. Amer. Med. Assoc., 1913, lxi, 59.

² E. R. Hayhurst, U. S. Bureau of Labor Statistics. Hygiene of the Painter's Trade, Bull. 120, 51, 1913.

³ L. I. Harris, Arch. of Intern. Med., 1918, xxii, 129.

⁴ U. S. Public Health Service Reports.

making of storage batteries and the enameling of sanitary ware are the most dangerous. Iron bath-tubs, sinks, and basins are heated to a red heat, then powdered with an enamel to which red lead has been added. The process is attended with exposure to great heat and to air heavily contaminated with enamel dust. In 1911 a group of 148 working enamellers was examined and 36 cases of undoubted plumbism found.¹ In storage battery plants, paste made of red lead or litharge is rubbed into the interstices of molded leaden grids. The rate of plumbism in this industry in 1914 was 17.9 per cent. The English rate was 2 per cent. and that for the great German factory at Hagen was 0.97 per cent.²

These are the principle sources of lead-poisoning and are, most of them, quite familiar to the ordinary physician. There are, however, some unusual ones which deserve mention. Among the cases of occupational disease reported by physicians to the Illinois Occupational Disease Commission were several girls with acute lead-poisoning who were found to have been dusting lead colors on prepared paper for lithotransfers, and applying aluminum foil to paper, this foil containing 7 per cent. lead. Cut-glass polishers were found to be using a paste consisting of 3 parts lead oxid to 1 part oxid of tin. Brass polishers, reported to be suffering from a peculiar form of brass-poisoning, proved to be breathing brass dust with a fairly high percentage of lead. In all, 70 industrial processes were found in Illinois which had given rise to lead-poisoning during the three years preceding 1911.

It seems necessary to lay so much stress upon the different lead trades because the factor of occupation is of great importance in making the diagnosis of industrial plumbism. If a man, known to be employed in work which exposes him to lead, begins to suffer from new symptoms of indigestion, abdominal distress, loss of strength, muscular pains, and vague nervous disturbances, the physician will not go far wrong if he decides that this is a case of industrial plumbism. In other words, the history of the man assumes a different significance if he is known to be exposed to lead. Industrial plumbism is rarely typical in its manifestations. Out of 70 cases examined by Apfelbach,³ but one exhibited the six so-called cardinal symptoms, lead line, pallor and anemia, gastric pain, constipation, tremors, and stippling of the red corpuscles. The physician who would wait for the development of a typical colic or palsy before making the diagnosis of lead-poisoning is said by Meillère to be as far astray as the man who would refuse to diagnose chronic alcoholism unless the patient had delirium tremens.

Brass-poisoning is really, according to our present state of knowledge, poisoning by the fumes of volatilized zinc. Brass is an alloy of copper and zinc, usually with lead in proportions of 1 per cent., or less,

¹ U. S. Bureau of Labor Statistics, Lead-poisoning in Potteries, Tile Works, and Porcelain Enameled Sanitary Ware Factories, Bull. 104, 1912, 59.

² U. S. Bureau of Labor Statistics, Lead-poisoning in the Manufacture of Storage Batteries, Bull. 165, 1915, 23.

³ G. Apfelbach, Amer. Jour. Med. Sci., 1918, clvi, 781.

up to 13 per cent. So far as we know, copper is negligible as an industrial poison. The zinc in the alloy has a low boiling-point and gives off fumes at about 300°C ., while copper does not volatilize till 1300°C . has been reached. Volatilized zinc is present when the molten alloy is poured into the molds in the brass foundry and is also encountered in zinc smelting, and in brazing, which means heating the edges of two brass surfaces until they fuse, in galvanizing which consists in dipping metal into a hot bath of zinc, and in the autogenous welding of zinc sheets. It is, however, much more common among brass founders than among workers in these other industries.

Lehmann¹ produced typical "brass founders' ague" in a brass worker, in himself, and in two of his assistants by exposure to pure zinc fumes. Zinc was recovered from the urine of these men. The symptoms consist in irritation in the throat with painful cough, a feeling of lassitude and weariness, with slight pains and stiffness in the limbs. Then, usually after some cooling of the body, either on leaving the hot foundry for the cold street or on undressing at night, a severe chill comes on and fever which Lehmann found to be about 102°F ., with a pulse of 106 and respiration 40 per minute. The chill is often very severe and is followed by sweating and a sense of profound exhaustion, but the next morning the man usually feels well enough to go back to work and it is rare that physicians ever see a case of uncomplicated industrial brass-poisoning. Those men who suffer enough to seek a physician's aid usually are victims of chronic plumbism complicated by acute attacks of brass-poisoning.

Although Lehmann's experiments were successful, they did not clear up the puzzling question as to the real nature of brass-poisoning. He points out several curious features with regard to it. In the first place, an amount of zinc which when administered as oxid through the air will set up typical ague would, if injected in soluble form subcutaneously hardly produce any noticeable symptoms. No other metallic poison produces an effect at all like brass-poisoning, which indeed resembles in some ways a bacterial infection with its incubation period, chill, fever, sweating, and sometimes evidence of widespread inflammation of the finer bronchioles. The resemblance to the anaphylaxis following injection of foreign proteins is also suggested by Lehmann, and he is inclined to believe that the zinc oxid when inhaled destroys the epithelial cells of the alveoli and that the symptoms are caused by absorption of proteins from these dead cells.

The brass industry is notoriously unhealthful, not only in this country, but in Great Britain. There are, however, many possible sources of occupational poisoning for the brass worker besides zinc oxid fumes. The presence of lead has already been mentioned and arsenic, phosphorus, antimony, and cyanids may be found as impurities. Cyanid fumes may arise from the potassium cyanid baths used in plating, and the so-called "pickling" by immersing brass in dilute sulphuric acid, may give rise to fumes of hydrogen arsenid if arsenic is

¹ K. B. Lehmann, *Arch. f. Hyg.*, 1910, lxxii, 358.

present in the alloy. The lacquers used are dissolved in various toxic volatile bodies and add other possible dangers to the work.

Mercury is mined in California. Whether or not there is mercurial poisoning among American miners as there is among the Spanish miners of Almaden and the Italian miners of Monte Amiata we do not know. Apparently no investigation in this field has been published. Metallic mercury is used in the making of thermometers and barometers, vacuum pumps, incandescent lights, and x-ray machines, in the course of which work mercury is likely to be scattered more or less over benches and floor coming in contact with the hands of the workers and, since it volatilizes at room temperature, contaminating the air. Mercury is used as amalgam by dentists and in gilding church crosses, buttons for naval uniforms, and ornaments for the outside of buildings. Fire gilding, as this use of amalgam is called, consists in applying mercury-gold amalgam and then driving off the mercury by heat. The resulting surface is very resistant to the stress of weather and the process is therefore used on objects which would be exposed to the weather. Metallic mercury is a constituent of solder used in the making of dry batteries and is a recognized source of mercurial poisoning in that industry.

There is a widespread use of the acid nitrate of mercury in the making of felt hats. Felt consists of matted hairs cut from the skins of rabbits, hares, beavers, etc., and it has been known for several centuries that the matting or felting process was greatly aided by a preliminary treatment of the skins with a solution of acid nitrate of mercury. This process, known as carroting, has been in use for more than two centuries and, although efforts have been made, especially in France, to introduce a non-poisonous substitute, they have so far failed.

Industrial mercurialism differs in its manifestations according to the amount of exposure. Acute poisoning is never seen, but in men exposed to the vapors of heated mercury, as in making thermometers, making and using soft solder, and gold or silver amalgam, the course of the intoxication is more rapid than in men who are exposed only to carroted fur in hat making. Stomatitis is very rare among hatters' furriers and hatters, but is often the first manifestation of the more rapid form. Mercurial tremors are characteristic of the slower form, but may also be present in the more rapid and the same thing is true of the psychic disturbances, insomnia, depression, loss of memory, loss of self-confidence, irritability, or nervous shyness. The mercurialism seen among hatters is often accompanied by anemia and emaciation and it is among these men that the motor disturbances are most severe. The tremor is very fine, observed first in the muscles of the tongue, lips, eyelids, and fingers. It is finer than the tremor of alcoholism and differs from senile tremor in that it subsides completely when the man is at rest. It is always an intention tremor, increased by observation and by attempts to control it; frequently a workman can continue at his usual task with much less difficulty than he experiences when he

tries to do some unusual thing like lighting a match or picking up a small object.

Martial found¹ in 1911, 60 per cent. of 250 hatters' furriers suffering from mercurialism. Gilbert² in 1912 found evidence of mercurialism in 43.6 to 66.67 per cent. of those engaged in the various processes of fur preparation. The records from England,³ Germany, Austria,⁴ and Italy are much more favorable, but the two published within recent years in the United States show a high rate of poisoning and some very extreme forms. In 1910 Mrs. Lindon W. Bates⁵ made an investigation of mercurial poisoning in New York City and discovered 80 cases of chronic mercurialism which had been acquired in the hatters' trade. Detailed histories were obtained of 59 in 40 of whom tremors were present, localized paralysis in 4, multiple neuritis in 5; in 14 there were psychic disturbances ranging from headache and insomnia to melancholia with suicidal tendency. Some of these cases represent as extreme forms of industrial mercurialism as can be found in the literature.

L. I. Harris⁶ of the New York City Health Department examined in 1917, 350 hatters' furriers and hat makers, and found 47, or nearly 14 per cent., with moderate or very marked tremor of arms, face, and tongue, and also marked gingivitis. Another 14 per cent. had moderate tremor with gingivitis accompanied in a number of instances by anemia and arteriosclerosis.

Arsenic trioxid, or white arsenic, the aceto-arsenite of copper, or Paris green, and lead arsenate are the compounds of arsenic used in industry. In the United States most of the arsenic is sublimed from the flue dust of the lead smelters, especially those in Utah and Colorado. It is also recoverable from copper ores, such as those mined in Montana and refined in New Jersey. The presence of large quantities of arsenic in these ores constitutes the most troublesome problem in the protection of the men against industrial poisoning, for although the damage done by lead is really much greater, the skin lesions set up by the arsenic are more immediately distressing and more productive of an excessive labor turnover than is lead-poisoning. Paris green is manufactured on a large scale, especially in Brooklyn and Chicago. It is a light fluffy powder, extremely difficult to control. Lead arsenate is increasing in importance as an insecticide. It is not so troublesome as Paris green and in the early days of its manufacture when it was sold as a paste there was apparently little poisoning among the men who handled it, but it is now sold dry and the danger is greater.

Arsenic trioxid is used as a constituent of sheep dip, as a preservative

¹ R. Martial, *Rev. d'Hygiène*, 1911, xxxiii, 224.

² Gilbert, *Internat. Cong. Hyg. and Demog.*, Brussels, 1903, v, Sec. 4.

³ F. E. Tylecote, *Internat. Cong. Hyg. and Demog.*, Washington, 1912. Lead-poisoning in the Smelting and Refining of Lead, iii, 778.

⁴ L. Teleky, A. Grotjahn, and J. Kaup, *Handwörterbuch d. soz. Hyg.*, Leipzig, 1912, 11, 735.

⁵ Mercury-poisoning in the Industries of New York City and Vicinity, *Nat. Civil Federation*, 1913.

⁶ L. I. Harris, *Dept. of Health, City of New York, Monogr. Series*, 1912, 5.

for skins, both bird and animal, as an ingredient for glass compounding, and for antifouling paint applied to the bottoms of ships. Cases of poisoning have been reported in Great Britain among men handling skins and hides, applying sheep dip, making and packing Paris green, and in this country from Paris green works and lead arsenate works, from lead and copper smelters, from copper mines, and from a tannery.

The typical skin affections caused by arsenic consist in patches of scleroderma, or warts, or horny patches with diffuse brown pigmentation, and these may later undergo slow cancerous change. When the arsenic dust falls on the more vulnerable surfaces such as the edge of the lips, the edge of the nostrils, the eyelids, the folds of the skin in axilla and groin, and the scrotum, inflammation with ulceration results. The same may occur in the throat, and the pressure of a cap across the forehead or of the edge of a respirator along the cheek may, by keeping the skin warm and moist and allowing the powder to settle there, result in inflammation and ulceration. Perforation of the septum of the nose is a fairly common accident in arsenic workers, but does not result in deformity as in syphilis, for the anterior part of the septum and the base are not involved. Hoarseness, with dryness of the throat, and cough are very common in arsenic workers.

The general symptoms resemble those of industrial plumbism, with colic and vomiting, but the loss of health and strength is not so great. In contrast to lead palsy there is a peripheral neuritis with paresthesias and severe neuralgic pains. The bronzing of the skin is another point in the diagnosis. The eyelids are first involved, then the temples, the neck, the axilla, and the skin around the nipples, until finally the bronzing may be general.

In connection with the consideration of skin lesions in arsenical workers it is proper to mention a theory which has lately been advanced concerning the well-known cancer of chimney-sweeps and briquet workers; namely, that the substance responsible for these malignant growths is not one of the coal-tar or petroleum compounds found in soot and pitch, but the arsenic which has been shown to be present in coal, especially in British coal (Delépine). Chimney-sweeps' cancer has never been prevalent outside of England. Observations made recently in a briquet works in Belgium¹ where several cases of epithelioma were discovered in a small working force and where arsenic was recovered from the coal dust and isolated from the urine of the men, form the latest contribution to this theory. An analagous situation was reported in 1913 from Germany. Miners of cobalt arsenid ore in the Schneeberg region of Saxony were said to have a startlingly high mortality from pulmonary carcinoma, and the cause was found in the arsenic dust.²

Arsenic-poisoning from wall-paper and textiles colored with arsenic greens apparently occurs from time to time still in Europe, as may be

¹ A. Bayet, and A. Slosse, *Comp. rend. Acad., d. Sc.*, Paris, 1919, clxviii, 704.

² A. Arnstein, *Verhandl. d. deutsch. path. Gesellsch.*, 1913, xvi, 332.

seen by recent English and Dutch reports, but the use of these colors is very rare in the United States and no instance of arsenical poisoning in textile or wall-paper makers or handlers has come to my knowledge. The Federal Department of Agriculture published in 1904 the results of analyses of 537 samples of wall-paper and only 4 had over 0.1 grain per square yard, the limit for wall-paper and textiles not used for clothing established by the Massachusetts Law of 1900.

A second form of industrial arsenical poisoning is much more serious and probably more common than those just discussed. This is poisoning by hydrogen arsenid, commonly called arseniuretted hydrogen, or arsin. It is a subtle and powerful poison with a rapid characteristic action, and yet the cases of poisoning escape detection for the most part, especially in this country where occupational disease is rarely studied with any degree of thoroughness. Arsin-poisoning is always accidental, unforeseen, because it is produced by arsenic which is not used in the particular industrial process, but only accidentally present and usually unsuspected.

It is because most metallic ores are arseniferous that this form of poisoning is a constant menace. The ordinary processes of smelting and refining do not rid the metal of all the arsenic and consequently commercial iron, zinc, lead, copper, antimony, are all likely to contain traces of arsenic, especially zinc and antimony. Commercial sulphuric acid is usually made by the chamber process from sulphur obtained by roasting iron pyrites, which is often contaminated with arsenic, and some of the arsenic passes over into the acid. Then if this acid is used to make hydrochloric acid from common salt the latter acid also may contain arsenic. There are innumerable industrial processes which require contact between hydrochloric or sulphuric acid and one of the heavy metals, and it is obvious that when this occurs the arsenic present in acid or metal, or both, may be liberated in the form of hydrogen arsenid, but because this is an accident for which no one is looking, the poisoning caused by it is likely to be ascribed to the wrong cause and the vague term "acid fumes" misleads the physician and the reading public.

It is safe to say that in all instances of mysterious illness occurring among workers with metals or acids, a search for arsin fumes should be made, for the following instances will show in how great a variety of processes an accidental evolution of these fumes may occur. Repairing or cleaning tanks in which acids have been stored has caused death from hydrogen arsenid in England, in Germany and Austria, and in the United States. Toy balloons are filled with hydrogen which is produced by the action of hydrochloric acid on zinc dust. English and German factory inspectors' reports tell of poisoning from this source. Several men in an English bleaching powder plant were poisoned cleaning out with an iron shovel a still which contained a small amount of arseniferous hydrochloric acid. Mild cases have developed in pickling, that is, dipping iron sheets in an acid bath, and in establishments using the electrolytic process for the recovery of copper.

Rambousek¹ tells of an instance of arsin-poisoning in the forming room of a storage battery plant. An extensive epidemic of poisoning from storage batteries made with a lead-antimony-arsenic alloy occurred in a British submarine and involved all but one of the crew of 50 men.² Noble W. Jones³ reported 5 cases, all severe and 2 fatal, in men engaged in the cyanid process for the recovery of gold and silver. The bed of zinc dust used in the process contained arsenic and the men inhaled arsin fumes. Another unsuspected source of these fumes is the making of coal-tar dye intermediates, especially benzidin and tolidin. A number of cases occurred in England in the early days of this industry just after the war and 5 in one plant in the United States during 1916.⁴ The American cases were never satisfactorily studied, but the English were thoroughly investigated and the presence of arsenic in the urine confirmed the clinical diagnosis (Wignall⁵).

Arsin-poisoning in industry is characteristically violent and rapid. The man is often "knocked out" in a few minutes, suffering from headache, dizziness, nausea, vomiting, pains in the epigastrium, and he notices that his urine is scanty and very dark, sometimes the color of port wine. In severe cases there may be within forty-eight hours symptoms which point to extensive destruction of the red blood-corpuscles, with consequent hematogenous jaundice, and the involvement of the kidneys increases. The urine becomes darker, there is albumin from the hemoglobin, the amount decreases, and there may be complete suppression. The red blood-cell count falls rapidly and strikingly, sometimes to less than 2,000,000. The jaundice increases, and there may be bronzing of the skin. In fatal cases, death may be caused by edema of the lungs or the man may pass into a typhoid state with tremors, delirium, ulceration of the mouth and throat. Hemorrhagic nephritis is found at autopsy and hemorrhagic inflammation of the liver. The mortality in industrial cases is said to be about 36 per cent. In those cases which go on to recovery the urine regains its normal color within a few days, but albuminuria may persist for some days and long after the acute symptoms have disappeared the anemia is still demonstrable. Wignall has shown that under proper treatment elimination of the arsenic by the urine takes from four to six weeks, but the actual return to health may take much longer.

Antimony is of very slight importance as an industrial poison. It is used in printers' type and in compounding rubber, especially medical rubber goods, the golden and crimson sulphids being used to give a reddish-brown tint to the rubber and to aid in vulcanization. There is little evidence of antimonial poisoning among printers, although some have attributed various nervous symptoms in printers to the presence of antimony in type metal. It may be responsible for the eczema from which the stereotypers sometimes suffer, or the traces

¹ J. Rambousek, *Industrial Poisoning*, tr. by T. M. Legge, London, 1913, 144.

² S. F. Dudley, *Jour. Industrial Hyg.*, 1919-20, 1, 215.

³ N. W. Jones, *Jour. Amer. Med. Assoc.*, 1907, xlviii, 1099.

⁴ A. Hamilton, *Jour. Industrial Hyg.*, 1921-22, 111, 16.

⁵ T. H. Wignall, *Brit. Med. Jour.*, 1920, 1, 826.

of arsenic which almost always accompany it may be responsible. Rubber compounders handle lead oxid and basic sulphate as well as antimony and whatever ill-health appears among them is likely to be referred to these compounds, although Carlson¹ has shown that the sulphids are soluble in human gastric juice to the extent of 3 to 8 per cent.

White phosphorus, which was formerly the most notorious of the industrial poisons, has now practically disappeared since the substitution of the insoluble sesquisulphid for white phosphorus in the making of lucifer matches. A few cases are reported from time to time in England from the one plant which produces white phosphorus, but none has come to light in the United States of late years.

Rarer Metallic Poisons.—Among the rarer metallic poisons are **vanadium, selenium, and cadmium.** Vanadium comes to this country from Peru in the form of a ground ore which is very dusty. It is used as ferro-vanadium in the making of ductile steel. The men exposed to the dust, and perhaps to the fumes from the alloy, are said to suffer from severe irritation of the respiratory tract, from anemia and consequent emaciation; albumin, casts, and blood are said to be found in the urine.² Industrial vanadium-poisoning has not, as yet, been satisfactorily studied and nothing positive can be said about it.

The same thing may be said of selenium which I have found handled in only one industrial plant as selenic acid and the sulphate. It whitens ordinary glass and is used also for ruby glass. Selenic acid is said to change to the methyl compound in the organism and the peculiar odor of the breath is the symptom most commonly noted by the workmen themselves and by the few physicians who have seen cases from this plant. There is said to be sometimes vomiting and pain in the abdomen and the lumbar region. The effect on the nose and throat is like that of a rose cold. This scanty description is all that I have ever been able to obtain with regard to selenium.

A recent article by G. Arbour Stephens³ tells of the recovery of cadmium, but no lead, in the liver of an old spelter workman in Wales who had been drawing compensation for chronic plumbism. The liver contained 0.91 grains of cadmium per pound and 0.77 of zinc. Six additional cases gave similar findings, although the quantity was not so large. Stephens believes chronic cadmium-poisoning is fairly common among spelter men. It resembles lead, but there is no typical colic. British calamin contains 0.5 to 1.5 per cent. of cadmium, Silesian calamin, 5 per cent.

Manganese-poisoning was first described by Couper⁴ in 1837, then lost sight of for many years. In 1901 von Jaksch described 3 cases, but believed them to be atypical forms of multiple sclerosis. A little later Embden reported 2 cases clinically identical with von

¹ A. J. Carlson, *Jour. Amer. Med. Assoc.*, 1913, lxi, 59.

² W. F. Dutton, *Ibid.*, 1911, lvi, 1648.

³ G. Arbour Stephens, *Jour. Industrial Hyg.*, 1920-21, 11, 129.

⁴ D. L. Edsall and C. K. Drinker, *Jour. Indust. Hyg.*, 1919, 1, 183.

Jaksch's and interpreted them correctly as manganese-poisoning in which view von Jaksch coincided. Other cases were added to the literature, bringing the number from European sources up to fifteen. In 1913 Casamajor published a report of 9 men employed in a dusty mill where manganese in the form of oxids and silicates is separated from other ore in part by the use of very strong magnets. These men presented the same peculiar and striking symptoms as those observed in Germany and, although at first Casamajor was not sure of the etiology, thinking that perhaps the strong magnetic field in which the men worked might be the cause of paralysis, he later came to regard them as due to manganese-poisoning. Then in 1919 Edsall and Drinker¹ described 39 cases, not all of advanced forms of poisoning, but all presenting suspicious or definite symptoms. All but one of the 48 American cases were exposed to manganese dioxid, the one exception being a man who for eight months shoveled Japanese manganese ore into a hopper.

The disease is unusually characteristic in its syndrome and the diagnosis is made with great ease. Edsall and Drinker summarize the phenomena as follows, in the order of their appearance: a history of work in manganese dust for at least three months; languor and sleepiness; stolid, mask-like facies; low, monotonous voice, economical speech; muscular twitching varying in degree from a fine tremor of the hands to gross rhythmic movements of the arms, legs, trunk, and head; cramps and stiffness in the calves usually at night after a day of exertion; slight increase in tendon reflexes, ankle and patella clonus, Romberg sign inconstant; retropulsion and propulsion; peculiar slapping gait, the patient keeping as broad a base as possible, involuntarily, to avoid propulsion; occasionally uncontrollable laughter, less frequently crying; absence of sensory, rectal, genito-urinary, or gastro-intestinal disturbances, of eye changes, of reactions of degeneration, of blood, urine, and spinal fluid alterations. The prognosis as to life is excellent, but no case of recovery from the paralysis is on record nor has any form of treatment any value. The prevention of manganese-poisoning consists in protection of the workmen against the dust.

Sulphuric Acid.—Of the heavy acids used in industry, sulphuric is the most important, nitric the most deadly. Sulphuric acid and sulphur dioxid, SO_2 , may be considered together for the SO_2 which is given off in burning coke, in producing gas from coal, in smelting lead and copper, and in bleaching processes, changes quickly in moist air to sulphurous acid and in contact with mucous membranes of nose and throat, to sulphuric acid. The effect, therefore, is essentially the same whether the workman breathes fumes of SO_2 or a finely divided spray of H_2SO_4 . Ogata and K. B. Lehmann,² testing various dilutions on human beings, found that irritation of the nose, eyes, and throat begins at as low a point as 0.01 parts in 1000 parts of air. Tolerance is,

¹ D. L. Edsall and C. K. Drinker, *Jour. Indust. Hyg.*, 1919, 1, 183.

² Ogata and Lehmann, *Rambousek's Industrial Poisoning*, tr, by T. M. Legge, London, 1913, 171.

however, quickly established and workmen can endure with no apparent discomfort an atmosphere which is very painful to the ordinary visitor. If the exposure is excessive, croupous inflammation of the bronchi with lobular pneumonia may be set up (von Jaksch), and a chronic catarrh is sometimes found after constant exposure to smaller quantities.

Sulphuric acid is used in an enormous number of industrial processes; for refining and bleaching tallow, refining sugar and starch, making glucose from starch, refining linseed oil, making fertilizer, cleaning and pickling metal, forming and charging storage battery plates, recovering metals by electrolysis, and as an aid in all nitration processes. It is, however, productive of comparatively little industrial poisoning aside from acid burns.

Nitric acid has far more damage to its credit than sulphuric or hydrochloric, especially of recent years. Up to 1914 the manufacture of nitric acid in the United States was not extensive, but it increased enormously during the years of the war, being in great demand for the manufacture of explosives. All explosives except gunpowder are nitrated products and their manufacture was attended with much poisoning from the fumes of nitric acid. Its peace-time uses are attended with much the same danger. Nitric acid is used in making celluloid, moving-picture films, dope for airplanes, in plating metals, in etching zinc and copper plates, and in various processes in the manufacture of coal-tar dyes. An accidental source of nitrogen oxids is the incomplete detonation of nitrated explosives when the blasting powders burn instead of detonating. This has been a prolific source of poisoning in the mines of the Rand (Irvine).¹

The usual way in which accidental poisoning from nitric acid and the oxids of nitrogen occurs is through a leak in the apparatus which allows the escape of the oxids and sometimes a fine spray of the acid. Haldane² found that half an hour's exposure to 0.05 per cent. of nitrogen oxid fumes was enough to kill mice, but death did not occur at once, not till after about twenty-four hours. The same thing is true of industrial poisoning, for, unfortunately, these gases are not immediately asphyxiating, as is chlorin, nor so burningly painful as SO_2 , and therefore the workmen often fail to realize their danger and stay long enough in the fumes to receive serious damage to the throat or lungs. These fumes cause inflammation of the mouth, the nares, the pharynx, and the larynx, but such injuries are usually masked by the much more dangerous damage to the lungs. There is at first a sensation of choking, of burning and smarting in the chest, then a strangling, spasmodic cough. If the man can get at once into the fresh air this bronchial spasm is usually quickly relieved by the ordinary first-aid treatment, a few drops of chloroform in hot water. Mild cases of this "fume sickness" were very frequent during the war, especially in summer. In one guncotton plant where records were kept there was an

¹ L. G. Irvine, *Brit. Med. Jour.*, 1916, 1, 163.

² J. Haldane, Quoted by Irvine.

average of 57 cases of nitrous fume poisoning in an average force of 600 men for each month from June 1st to October 1st.

Experience soon taught the physicians attached to these plants that an apparently mild case might turn to a very serious one within a few hours. There were many records of men who apparently recovered from the effects of the exposure to fumes, went home, ate supper as usual, went to bed and then woke with a sense of choking, and within a few hours were dead from edema of the lungs. According to Hudson¹ of the Du Pont Company, the pneumonia which develops in slower cases is lobar in type and follows the usual course, only that it is likely to be less severe except in men who have a latent tuberculosis when it may result in lighting up the infection. During the one year of explosives manufacture, ending November, 1916, a Federal investigation brought to light some 1400 cases of nitrogen oxid poisoning with 28 deaths.²

The most illuminating American study of the after-effects of this form of poisoning among workmen was made by Hall and Cooper,³ who were able to observe 20 men poisoned by nitrous fumes from a broken carboy of nitric acid. Two died from the immediate effects, two from pneumonia developing twenty-two days and thirty days later. Nine months after the accident, 11 of the 16 surviving men had not yet regained their usual health, but complained of shortness of breath, cough, pain in the chest and loins, gastro-intestinal disturbance, and nervousness. Loss of weight was general, ranging from 20 to 40 pounds.

Hydrochloric Acid.—According to Lehmann,⁴ diseases of the respiratory passages and of the digestive organs are unduly prevalent among men engaged in the manufacture of hydrochloric acid. The fumes are very irritating, even caustic, to the lips and tongue, and eroding to the teeth. The safety limit is said to be between 0.1 and 0.2 per thousand volumes of air.

Chlorin fumes may be given off in the early stages of nitric acid manufacture if sodium chlorid is present in the sodium nitrate, in the manufacture of hydrochloric acid, in the electrolytic production of chlorid of lime from common salt, in one method of producing soda, in bleaching paper, and in some processes of dye manufacture. It does not cause much industrial poisoning, perhaps because it is so asphyxiating that workmen find it intolerable and escape as quickly as possible. The greatest amount of exposure in American industry is probably in the making of chlorid of lime by passing gas into small closed chambers covered with a thick layer of powdered lime. Emptying these chambers and packing the barrels involves exposure to heavy fumes, but we have no idea what effect this has upon the workmen. Leymann, in⁵ writing

¹ W. G. Hudson, *Med. Rec.*, 1917, xci, 89.

² A. Hamilton, *Jour. Amer. Med. Assoc.*, 1917, lxxviii, 1445.

³ J. N. Hall and C. E. Cooper, *Jour. Amer. Med. Assoc.*, 1905, xlv, 396.

⁴ K. B. Lehmann, *Arch. f. Hyg.*, 1886, v, 1, and 1899, xxiv, 272.

⁵ Leymann, *Rambousek's Industrial Poisoning*, tr. by T. M. Legge, London, 1913, 28.

of a German plant which is far better than any in the United States, states that 17.8 per cent. of the chlorid men suffered from respiratory troubles and only 8.8 per cent. of the other men in the same plant.

Hydrocyanic acid and the cyanids are of increasing importance in industry. The acid has come into extensive use for the destruction of vermin as, for instance, in the Port of New York, the gas being sent into ships through pipes and driven out by compressed air. According to Koelsch⁴³ its use for this purpose in Germany forms a new problem in industrial hygiene because it endangers not only the disinfectors, but the men who work in the disinfected rooms. He recounts several fatal accidents during and after disinfection. It is possible, also, that hydrocyanic acid, or cyanogen, plays a larger part than has been realized in the poisoning from illuminating gas, blast-furnace gas, the distillation of coal-tar, the manufacture of Prussian blue, and in the deaths which follow exposure to burning celluloid.

Chronic cyanid-poisoning seems to be rare and the cases which are reported come from factories in which galvanoplasting is carried on with gold or silver in a cyanid bath (Koelsch,¹ Merzbach,² Tatham³). Collins and Martland⁴ described a case of rapid and intense intoxication involving the spinal cord in a man who was exposed to the fumes of a potassium cyanid tank and had his hands continually wet with the fluid. Cyanogen chlorid has, according to Reed,⁵ produced a fairly definite clinical picture in men breathing small amounts over a fairly long period. He produced much the same symptoms in animals and found that the chronic effect of cyanogen chlorid is more severe than that of the more common cyanids or of hydrocyanic acid.

Calcium cyanimid is produced at a stage in the recovery of atmospheric nitrogen and also for use as a fertilizer. Industrial poisoning in nitrogen recovery plants occurred in France and in the United States during the war and several reports from Italy show that the peasants who use it for fertilizer have suffered from very distressing skin lesions. The powder is very caustic and severe cellulitis, even abscesses, result when it falls on sweating skin. Severe lesions are produced also on the mucous membranes of the nose, mouth, and throat. Langlois⁶ in France, and Lampton of Barksdale, Wisconsin,⁷ both described a pronounced vasomotor depression with flushing, sweating, rapid pulse, headache, dyspnea, and ringing in the ears in calcium cyanimid men who indulged in even a very small amount of alcoholic drink.

Potassium and sodium bichromate are used extensively in tanning by the rapid American method, as mordants in dyeing and printing, in making lead chromate, in oxidizing anthracene to make

¹ F. Koelsch, *Zentralbl. f. Gewerbehyg.*, 1920, viii, 93.

² G. Merzbach, *Hyg. Rundschau*, 1899, ix, 45.

³ Tatham, *Brit. Med. Jour.*, 1884, i, 409.

⁴ Collins and Martland, *Jour. Nerv. and Ment. Dis.*, 1908, xxxv, 417.

⁵ C. I. Reed, *Jour. Industrial Hyg.*, 1920-21, ii, 140.

⁶ J. P. Langlois, *Bull. de l'Acad. de Med. (Paris)*, July 9, 1918.

⁷ Lampton, see A. Hamilton; *Jour. Industrial Hyg.*, 1919-20, i, 211.

alizarin colors, and in photography and in photo-engraving. There is a characteristic effect on the skin and mucous membranes from a local caustic action which is slow and almost painless. The ulcers are seen especially in the nares, they are large and indolent and slow to heal, perforation of the septum is common. Legge¹ found it in 71.6 per cent. of 176 English chrome workers, but Leymann² found ulcers and perforated septum in only 30.5 per cent. of 722 German chrome workers. Gilman Thompson³ describes an American case with perforation of the septum, clogged nostrils, offensive breath, loosened teeth, inflamed throat, and nausea, which at first seemed to come only from excessive efforts to clear his throat, but later seemed to be independent.

Hydrogen sulphid, or sulphuretted hydrogen, is a recognized danger in certain industries, such as the making of sulphur dyes, especially the browns and khakies, the manufacture of sulphur monochlorid, and of the new parasitoid, trisulphid of barium. The cases reported are far from numerous, but they make their impression on the men engaged in dye and chemical manufacture because they occur with such startling rapidity. Apparently the man who breathes sulphuretted hydrogen and is "knocked out," either dies without recovering consciousness or comes to in a couple of hours and seems none the worse for it.

Carbon disulphid is not so important in American industry as in Germany, France, or Great Britain, where it is much more extensively employed in the vulcanization of rubber than it is in the United States. We use it in liquid or in vapor form to vulcanize dipped rubber goods, such as surgical gloves, toy balloons, rubber dam and thin sheeting, finger cots, bathing caps, cheap rubber clothing, and sometimes hot water bottles and nipples. It is also used, but not always, to splice the inner tubes of automobile tires. A second industry in which it is found in the United States is the manufacture of artificial silk by the so-called Viscose process.

The French and German literature is full of discussions of the effects of carbon disulphid, especially in rubber workers. It is regarded as a specific poison to the central nervous system, causing paralysis and insanity, although Marie held that the manifestations were to be explained as hysterical and that carbon disulphid was only the exciting cause of a pre-existing hysteria. Peterson⁴ in 1887 saw 3 cases of insanity from a New York rubber factory. Jump and Cruice⁵ reported 2 cases of insanity from an artificial silk factory in Pennsylvania, and Heath,⁶ of Indianapolis, saw a case of optic atrophy in a woman who had worked for two months using carbon disulphid in splicing inner tubes. Cases are, however, far from common in this country and tend

¹ T. M. Legge, Ann. Rep. Chief Inspector Fact. and Workshops for Year 1912, 146.

² Leymann, Rambousek's Industr. Pois., tr. by T. M. Legge, London, 1913, 56.

³ W. G. Thompson, The Occupational Diseases, New York, 1914, 18.

⁴ F. Peterson, Boston Med. and Surg. Jour., 1892, cxxvii, 325.

⁵ H. D. Jump and J. M. Cruice, Univ. Penn. M. Bull., Phila., 1904, xvii, 193.

⁶ F. C. Heath, Ann. Ophthal., 1902, vi, 4.

to be even rarer as tetrachlormethane, which is non-inflammable, tends to displace the very inflammable disulphid. Hayhurst¹ states that only about 1 per cent. of the 100,000 rubber workers in Ohio are exposed to carbon disulphid.

Carbon monoxid is encountered in industry in steel mills, especially in blast-furnace operation, and repairing and cleaning flues and mains; in making illuminating gas, carburetted water gas, producer gas, etc., and using industrial gases in smelting ores, metallurgical processes, glass works, bakeries, kilns, enameling furnaces, and other industries in which gas is used as a source of heat or power. It is encountered also in making the by-products of coke, in mines as a result of explosion, and in the exhaust gases from motor cars and engines. Industries in which small amounts of carbon monoxid may be present are canneries, printing shops, metal casting and soldering from the gas used to melt metals, tailor shops from the gas used to heat irons, and interior decorating when gas salamanders are used to dry out the walls. The gas from blast-furnaces is said to contain from 26 to 50 per cent. carbon monoxid; producer or power gas, 23 per cent.; the gas in coke by-products works from 6 to 40 per cent.; and illuminating gas from 5 to 30 per cent. according to the proportion of water gas added. The exhaust gases from motor engines were found by Henderson² to contain from 5.5 to 6.8 per cent. CO.

Acute poisoning with carbon monoxid is of fairly frequent occurrence in steel works, although the fatalities from this cause have been lessened during recent years in the United States. It is also a fairly frequent occurrence in metal mines where blasting goes on continuously, as is true in the copper mines of Montana and the iron mines of Alabama, but in coal mines blasting is as a rule not continuous and carbon monoxid is a danger only in case of explosion or mine fire. If the mine is poorly ventilated, the gas may remain in the fine dust after an explosion and affect the "muckers" who gather it up. Cleaning the mains in steel mills, which involves stirring up the dust, is apparently productive of even more gassing than tending the blast-furnaces.

The workman who is overcome by gas may lose consciousness almost instantaneously and in many instances the actual cause of death is a fall from a platform or the top of a furnace. Usually, unless the dose is overwhelming, there are warning symptoms, dryness in the throat, a sweetish taste, pressure in the head with confusion or drowsiness, a feeling of weakness in the knees, and of general lassitude, more rarely pain in the stomach. Complete loss of consciousness does not often take place except in mine accidents. Apfelbach³ says that only 65 of 261 men gassed in Illinois steel mills lost consciousness. He also found that the supposedly typical rosy red cheeks and lips were actually

¹ E. R. Hayhurst, *Diseases of Occupation and Vocational Hygiene*, Kober and Hanson, Philadelphia, 1916, 36.

² Y. Henderson, H. W. Haggard, M. C. Teague, A. L. Prince, and R. Wunderlich, *Jour. Industrial Hyg.*, 1921-22, iii, 137.

³ G. Apfelbach, *Diseases of Occupation and Vocational Hygiene*, Kober and Hanson, Philadelphia, 1916.

the exception, pallor and lividity the rule. Convulsions are rare, but delirium following the stage of coma is said by some American physicians to be fairly common.

Studies in the blood of steel workers exposed more or less continually to carbon monoxid were made by Haines, Apfelbach, and Karasek,¹ who found polycythemia as the typical condition. Six hundred and sixty-five men were examined and the counts ran from 6,000,000 to 9,676,000, the hemoglobin from 95 to 125 per cent. In this their findings correspond with those produced experimentally by Nasmith and Graham.² On the other hand, the Illinois Steel Company reported that 175 red blood-cell counts taken at Gary and in South Chicago on men who had worked in the blast-furnace and open-hearth departments for years showed that only 2.2 per cent. had counts over 6,000,000 (personal communication).

British, German, and French literature contains numerous instances of severe lesions following industrial poisoning with carbon monoxid: pneumonia, lesions of brain and cord, of the heart, of the optic nerve, of the digestive system, and of the vascular system. In fact, according to Lewin,³ of Berlin, there is no poison which is known to give rise to so wide a variety of pathologic conditions as is carbon monoxid. It is only very recently that any attention has been turned in this country to the after-effects of industrial carbon monoxid poisoning, and even now little that is positive can be said about it. Dr. H. S. Forbes⁴ made an extended inquiry in 1920 in the endeavor to discover whether miners and metal workers in the United States suffered from serious sequelæ after being overcome with CO. He covered the metal mines, coal mines, blast-furnaces, and producer gas boilers and engine rooms in Montana, Colorado, Oklahoma, Arkansas, Alabama, Tennessee, Kentucky, and Pennsylvania, but he found that although acute gassing is fairly common there are almost never any serious after-effects unless there has been a pre-existing pathologic condition. A young healthy adult severely gassed by "white damp" or blast-furnace gas either dies or recovers entirely. Nor did he find any evidence of a cumulative effect from frequent exposure to smaller quantities.

The accidents which occur in garage work and from illuminating gas do, as is shown abundantly in medical literature, set up changes in brain and cord which may be more or less lasting. The recent work of Yandell Henderson⁵ and his colleagues suggests that the cause for this difference between illuminating and exhaust gases and other carbon monoxid containing gases is to be found in the presence of constituents in the form of gas of which benzene is probably the most important. It is impossible to feel, however, that we are as yet in a position to explain satisfactorily the absence among American miners and steel men of serious mental impairment, paralyses, arteriosclerosis, etc., which

¹ Report of [Illinois] Commission on Occupational Diseases, 1911, 89.

² G. G. Nasmith and D. A. L. Graham, *Jour. Physiol.*, 1906-07, xxxv, 35.

³ L. Lewin, *Die Kohlenoxydvergiftung*, Berlin, 1920, 189.

⁴ H. S. Forbes, *Jour. Industrial Hyg.*, 1921-22, 111, 11.

⁵ Henderson et al., *Jour. Ind. Hyg.*, 1921-22, iii, 137.

according to European observers are such common sequelæ of exposure to carbon monoxid in industry.

Phosgene.—The war literature contains so much on phosgene-poisoning that it is unnecessary to go into details as to its action as an industrial poison. The German Factory Inspection reports before the war mentioned from time to time cases of phosgene-poisoning, rarely fatal. It is used in the preparation of Michler's ketone, an important dye intermediate, and in the United States it had never been heard of till the growth of the dye industry in 1916 led to its production. Much secrecy was observed with regard to it, especially as it was later manufactured for use in gas warfare. I had reason to believe that the reports which were made to me of 3 deaths were beyond doubt, but rumors of several other deaths could not be verified.

Aliphatic Series.—The petroleum products are extensively used in industrial processes and the greater number of them are known to be productive of injury to the skin or the central nervous system. The heavier petroleum distillates give rise to acne and sometimes multiple skin abscesses. Workmen in refineries are the ones chiefly exposed, but the use of the heavy oils in preparing bindery twine and in cleaning printing press rollers is productive of slighter forms of skin disease. The lighter distillates, naphtha and benzine, are used extensively as solvents for rubber and fats and as a substitute for linseed oil. Consequently the workers who are exposed to contact with naphtha and benzine and to their fumes are employed in making dipped rubber goods, spread rubber goods, using rubber cement, using the so-called quick drying paints, and working in dry cleaning establishments. In all these industries a mild form of acute poisoning from naphtha is a familiar occurrence. Chronic poisoning does not give rise to a typical clinical picture and is not often recognized, but undoubtedly it exists among rubber workers, dry cleaners, and varnishers who work continually in an atmosphere contaminated by these fumes. The increasing expense of the petroleum products and the increasing cheapness of the coal-tar distillates, benzene and toluene, is leading to the substitution of the latter, especially in rubber factories, thereby greatly increasing the danger to the workers.

Alcohols.—The only alcohols which are industrially important are ethyl and methyl, although amyl alcohol is sometimes used as a solvent. Methyl alcohol has been a source of very serious poisoning in American industry, both through inhalation of fumes and absorption through the skin. The most conspicuous cases have arisen in connection with the application of shellac to the interior of brewery vats, but blindness and death have also occurred in other trades in which wood alcohol was used as a solvent. The manufacture of the alcohol does not seem to be attended with danger, only its use. It enters into the composition of varnish and airplane dope, of paint and varnish removers, it is used to dehydrate nitrocellulose for celluloid, and to make dye intermediates. Wood alcohol poisoning among men employed in the stiffening of felt hats, which used to be notorious, has ceased since

denatured alcohol has taken its place. It must be borne in mind, however, that there are also dangers in connection with denatured alcohol, for the American law allows the denaturing of grain alcohol by the addition of wood alcohol up to 20 per cent. and cases of poisoning have been reported from Germany and Bohemia following the use of alcohol with only 2 per cent. of methyl alcohol, in the United States from the use of a 4 per cent. mixture.¹

Chlorin Derivatives.—The chlorin derivatives of the fatty series which are used in American industry are tetrachlorethane, a powerful solvent for cellulose acetate, and tetrachlormethane commonly called carbon tetrachlorid. The former came into prominence during the war when great quantities of cellulose acetate were used in airplane dope and this solvent gave rise to severe poisoning among the dopers in Germany and England. The Germans quickly abandoned its use, but the British were unable to find a substitute for the first two years and they reported in January, 1917, no less than 70 cases of toxic jaundice, 12 of them fatal, besides many more of less serious forms of poisoning.² Profiting by the British experience, we did not use this dangerous substance on our airplanes, but it has recently come into use in the making of artificial silk from cellulose acetate and for the production of non-inflammable moving-picture films. Great precautions are necessary in factories which use this highly toxic substance. Tetrachlormethane,³ which is said by British experimenters to be twice as toxic as chloroform, by the Germans only one-half as toxic, is the chief constituent of a popular fire extinguisher, a non-inflammable cleansing fluid for gloves and clothing, and is used somewhat as a solvent for sulphur monochlorid in vulcanizing the inner tubes of automobile tires, instead of the more efficient carbon disulphid which is inflammable. It is apparently more irritant to the respiratory tract than is chloroform and severe bronchitis with bronchopneumonia has followed the use of this fire extinguisher in an enclosed place. Vulcanizers complain of irritation of nose and throat, but it is so much less toxic than carbon disulphid that its introduction for tire splicing is a distinct advantage.

Trichlorethylene has been used in Germany as a solvent of fats and oils and there is a report of four instances of poisoning among men using it in open cans.⁴ There were symptoms of irritation of the central nervous system, burning of the eyes and hands, and then a sudden onset of complete sensory paralysis of the three branches of the trigeminus on both sides, all parts of the head supplied by the spinal nerves being quite normal. The cornea was absolutely anesthetic, but no keratitis followed, although the anesthesia in one case lasted four months. There was loss of the sense of smell and the ability to taste sweets. One man lost 14 teeth and 3 had disturbances of vision which

¹ Robinson, Jour. Amer. Med. Assoc., 1918, lxx, 148.

² A. Hamilton, Monthly Review, U. S. Bureau of Labor Statistics, 1918, vi, 289.

³ U. S. Bureau of Labor Statistics, Bull. 179, 1915, 5.

⁴ Plessner, Berl. klin. Wehnschrift., 1916, xxxiii, 35.

were attributed to the injury to the nervi nervorum coming from the trigeminus.

Methyl Bromid.—A very peculiar form of poisoning is reported from Germany as set up by contact with methyl bromid and by breathing the fumes. In 1920 three articles appeared in German^{1, 2, 3} describing 10 instances and referring to 13 others formerly reported from the same country. The history of these cases shows that there is always a free interval, from twenty-four hours to a week, between the exposure and the onset of symptoms. Then suddenly the man is seized with muscular contractions, excitement passing into mania or stupefaction, epileptiform convulsions, coma, and death, or slow recovery with neurosis and psychosis persisting many weeks. Autopsy on fatal cases shows excessive changes of the cortex of the brain. The peculiar phenomena consist in the latency of the poison, the deep and irreparable lesions in the central nervous system, and the fact that methyl bromid has never been recovered from the blood or organs. Löffler and Rüttimeyer exposed guinea-pigs to fumes and found that if the animal was killed immediately methyl bromid could be recovered, but that it might disappear if the animal were allowed to live as long as half an hour.

Dimethylsulphate is used in dye manufacture to produce the important intermediate, dimethylanilin. It was one of the gases selected by the Germans for possible use in trench warfare and their attention had evidently been called to it by 3 severe cases of poisoning, 2 of them fatal, which had occurred in two dye works and which were studied and reported by Weber⁴ of Schmiedeberg's laboratory. The action of dimethylsulphate is locally caustic, the mucous membranes of larynx, trachea, and bronchi being destroyed and a bronchitis with pneumonia following, then involvement of liver and kidneys. There is also intense inflammation of the eyes and, in the one case in which dimethylsulphate was spilled on the skin there were extensive burns. Recently 2 similar cases, but not fatal, have been reported by F. D. Mohlau⁵ of Buffalo. These men were exposed to the fumes and suffered from inflammation of eyes, throat, and respiratory tract. One of them was delirious and then comatose and relapsed several times during recovery from his pneumonia with an aggravation of all symptoms. Both men at the time of writing, some six weeks later, were suffering from photophobia and one had complete loss of color vision and his visual field was reduced to one-tenth.

Amyl acetate is called by the workmen banana oil, and is an important ingredient of solvents for shellacs and varnishes, for varnish removers, airplane dope, and celluloid. Tested by Lehmann⁶ and by Koelsch⁷ it has been found to cause irritation of the eyes and the

¹ F. Rohrer, *Vierteljahrsschrift f. gerichtl. Med.*, 1920, lx, 51.

² E. Goldschmid and E. Kuhn, *Zentralbl. f. Gewerbehyg.*, 1920, viii, 28.

³ Löffler and Rüttimeyer, *Vierteljahrsschrift. f. gerichtl. Med.*, 1929, lx, 60.

⁴ S. Weber, *Arch. f. exper. Path. u. Pharmacol.*, 1902, xlvii, 113.

⁵ F. Mohlau, *Jour. Industrial Hyg.*, 1920-21, ii, 238.

⁶ K. B. Lehmann, *Arch. f. Hyg.* 1913, lxxviii, 260.

⁷ F. Koelsch, *Ztschr. d. Zentralstelle f. Volkswohlfahrt*, 1912, xix, 246.

mucous membrane of nose and throat, and also headache, dizziness, slight confusion. Inquiry among men employed in varnishing and doping shows that banana oil is held responsible for the very decided discomfort and sometimes actual illness from which these men suffer, but the solvents which contain amyl acetate usually contain also substances more highly toxic, such as benzene and methyl alcohol, and it is probable that the amyl acetate plays a relatively insignificant rôle.

Aldehyds.—A few of the aldehyds are important in industry. Formaldehyd is manufactured for use as a disinfectant, and cases of bronchitis and even bronchopneumonia are reported by physicians practising near the largest American plant producing formaldehyd. It is combined with phenol to make bakelite, a substance very like hard rubber, and with ammonia to make hexamethylenetetramin, which is used not only as a medicine, but as an aid to the vulcanization of rubber. Both of these compounds are irritating to the skin and set up a very troublesome trade dermatitis. Acrylic aldehyd, or acrolein, is an exceedingly irritating gas given off when fats are rendered, in candle making, in soap factories, and when old printers' type covered with oily ink is melted down in the stereotype kettle, or the melting pots in the composing room. The experiments of Iwanoff¹ and of Lewin² show that acrolein is not only immediately distressing, but may give rise to inflammation of pharynx and bronchi, abdominal pain, and diarrhea. These facts are well known to printers and they avoid if possible the fumes which arise during the early stages of melting down old type.

Acetone.—Industrially acetone, or dimethylketone, has not shown itself to be toxic. It is used in large quantities as a solvent, for dopes and varnishes, and for the production of smokeless powder, but I have seen no evidence of any harm arising from its use.

Ether.—Sulphuric ether, which was used in great quantities during the war in dehydrating nitrocotton for smokeless powder, caused many cases of mild ether-poisoning to which women seemed distinctly more susceptible than men. There was also evidence of loss of health among those who were employed as long as six months, and Minot found an increase of the red cell count together with a low hemoglobin, these changes being much more pronounced among the women than among the men.³

Nitroglycerin has a curious history as an industrial poison. Men who are engaged in its manufacture and in the preparation of dynamite are exposed to fumes and absorption through the skin, but strangely enough they do not show the vasodepressant effect that one would expect.⁴ It is true that when they first go to work they are likely to suffer from headache which may be intense enough to make them actually delirious, but most of them acquire immunity within a fairly

¹ N. Iwanoff, *Arch. f. Hyg.*, 1911, lxxiii, 307.

² L. Lewin, *Arch. f. exper. Path. u. Pharmacol.*, 1900, xliii, 351.

³ A. Hamilton and G. R. Minot, *Jour. Industrial Hyg.*, 1920-21, 11, 41.

⁴ Ebright, *Jour. Amer. Med. Assoc.*, 1914, lxii, 201.

short time and, provided they do not go off on a vacation, they reach the point where they can absorb daily an amount from twenty to thirty times the medicinal dose, yet without any apparent effect on the heart or circulation. However, very hot weather may break down this immunity and it is quickly lost by a short absence from work. Laws¹ describes the symptoms of an acute attack as follows: There may be warning in a sudden blindness in one or both eyes, then when the headache begins sight returns, there is a feeling of fear, flushed face, the heart is rapid, later markedly slow, headache is intense, lying down may be unbearable, sleep impossible, there is nausea and vomiting, and large quantities of low gravity urine are passed. The "powder men" are said to become easily intoxicated and alcohol certainly increases the severity of an attack of poisoning. No chronic effects were noted by Laws or by Ebright.

Aromatic Series—Benzene or Benzol, Etc.—Coal-tar distillates and their derivatives were not extensively used in the United States before the war and were not produced in this country at all. Since 1914 there has been an extensive production of benzene and toluene, first for the manufacture of explosives, then as solvents to take the place of petroleum benzine and naphtha, as crudes for the production of coal-tar dyes and of anilin, for use in rubber manufacture, and finally as a substitute for gasoline in motor car fuel.

Cases of industrial poisoning from the coal-tar distillates were very rare in the United States before 1914. It is true that Selling's² famous cases from a Maryland cannery were published in 1910, but after that there is nothing in the literature of any importance until after the outbreak of the war. Then came the shutting off of the German supply and the coincident demand for benzene and toluene. During the war benzene was used in the production of phenol for picric acid (trinitrophenol), of mononitrobenzene which is an intermediate for the production of anilin, and of dinitrobenzene for use as an explosive. Toluene was used to make trinitrotoluene. At the close of the war the sudden cessation of the demand for explosives obliged the coke by-products industry to seek other markets for these distillates and they were found in dye works, rubber works, shoe factories, the making of varnishes and varnish removers, of quick drying paints, and of cement for artificial flowers. In all of these industries petroleum naphtha and benzine were formerly used, but benzene and toluene are much more powerful solvents and at the same time have become decidedly cheaper. Their cheapness is the reason why they are also to be found mixed in varying proportions with petroleum gasoline for motor car fuel.

This change in American industry is greatly to be deplored. Benzene has already since the war caused a number of sudden deaths in industry and of deaths from chronic poisoning. In mild cases of acute poisoning there is a condition resembling early alcoholic intoxication, with excitement, sometimes combativeness, sometimes exhilaration,

¹ Laws, Jour. Amer. Med. Assoc., 1910, 1, 793.

² L. Selling, Johns Hopkins Hosp. Bull., 1910, xxi, 33.

then headache, dizziness, depression, followed by general malaise, loss of appetite, and nausea, sometimes vomiting. If the exposure is great, as happens when a man is obliged to enter a still or tank to make repairs, or when there is an overflow, the effect of the fumes is very rapid and the man becomes delirious, shouts and sings, and may so hinder the efforts of his rescuers to get him out of his dangerous position that he brings about his own death or that of one of the rescuing party. Loss of consciousness succeeds the delirium, the respiration is rapid and shallow, the pulse weak and rapid, and convulsions may precede death. During the war three instances were related to me of immediate collapse, and death within a few minutes, apparently from paralysis of the respiratory center.¹

The cases described by Selling and the similar ones reported by McClure² and by Harrington³ were typical chronic poisoning, with leukopenia, a marked, but less marked, loss of red corpuscles, and capillary hemorrhages giving rise to bleeding from the gums, nosebleed, hemorrhage from stomach or intestines, and purplish spots over the skin. Such cases have so far been reported in the United States from factories using a solution of rubber in benzene, as a sealing mixture for cans, and as a cement in making rubber footwear. Experimental poisoning with benzene carried out by Hektoen⁴ and by Rusk⁵ show that benzene attacks the tissues and cells that are concerned in the production of antibodies. There is a diminution in lysins and precipitins, together with grave lesions in the bone-marrow, leukopenia, and a reduction in the phagocytic power of the blood. These results have an important bearing on industrial poisoning.

The most important derivatives of benzene and toluene are the nitro-, amido-, diamino-, and chlor- compounds used in the production of coal-tar dyes, drugs and perfumes, and in the manufacture of rubber. In considering their toxicity in industry, note must be taken not only of the chemical structure but of the physical, for solids are less dangerous than fluids and those that volatilize readily are attended with much more danger than those which do not. Their use in industry may or may not involve exposure and this means that a very toxic substance may give rise to less trouble than one which is not highly toxic, but has to be handled a great deal. One would expect that phenol would be among the most troublesome, but actually industrial poisoning from phenol is practically unknown except for an occasional burn. Mononitrobenzene is more highly toxic than dinitrobenzene and is fluid while the latter is solid, yet dinitrobenzene causes far more poisoning because it is handled so much more.

The entrance of chlorin into an aromatic compound changes it very little. Chlorbenzene seems to be somewhat less toxic than benzene.

¹ A. Hamilton, *Industrial Poisons Used or Produced in the Manufacture of Explosives*, U. S. Bureau of Labor Statistics, Bull. 219, 1917, 15.

² R. D. McClure, *Jour. Amer. Med. Assoc.*, 1916, lxxvii, 793.

³ T. F. Harrington, *Boston Med. and Surg. Jour.*, 1917, clxxvii, 203.

⁴ L. Hektoen, *Jour. Infect. Dis.*, 1916, xix, 69.

⁵ G. Y. Rusk, *Univ. Calif. Pub. Pth.*, 1914, ii, 139.

The entrance of HO renders the naphthols, alpha and beta, more irritating than is naphthalene. The nitro and the nitroso group always increase toxicity whether they enter the ring or a side chain, but there is no rule as to increasing toxicity with an increasing number of NO₂ groups, in fact the 1-2-4 isomer of dinitrophenol which was used in large quantities as an explosive by the French proved to be far more toxic than trinitrophenol, picric acid.¹ Reduction of NO₂ to NH₂ lessens toxicity, anilin is less toxic than nitrobenzene and if it is sulphonated it is rendered quite harmless. The entrance of COOH may have the same effect as the sulphonic group. Nitrobenzoic acid is harmless. The acetyl group and an alkyl group lessen the toxicity, acetanilid is less poisonous than anilin, and so is dimethylanilin.

According to men with experience in the dye industry, paratoluidin is more poisonous than ortho, paranitranilin more dangerous than meta, and orthonitrochlorbenzene more toxic than para, the meta isomer coming last. As to the phenylendiamins, there is a difference of opinion, some holding that the para position is the worst, others the meta. On the whole, of the nitro compounds dinitrobenzene and dinitrochlorbenzene are the most troublesome in the dye industry, trinitrotoluene and dinitrophenol 1-2-4 in the explosives industry. Anilin and the two toluidins are the most important of the amido compounds and seem to be about equally toxic.

Abundant observation in the manufacture and use of these intermediates shows that absorption takes place chiefly through the skin even in the case of those that are highly volatile. Cases of poisoning do arise from exposure to fumes alone, but serious poisoning is apparently always caused by direct contact. The symptoms in general (with the exception of DNP 1-2-4) depend on methemoglobin formation and consequent internal suffocation, with subsequent evidence of red blood-cell destruction: Anemia, immature forms of red corpuscles, slight jaundice. The urine is darker and contains a reduction product which, in anilin-poisoning, is para-amidophenol. A typical industrial case has the following history: After a period of general discomfort, indigestion, loss of appetite, irritable temper, depression, headache, breathlessness on climbing stairs, and a characteristic cyanosis of the face and lips which is easily recognized by experienced men, the man undergoes an acute attack which begins with sudden flushing of the face, a feeling of fulness in the head, roaring in the ears, a sense of weakness in the knees, abdominal pain, sometimes nausea and vomiting. The flushed face then becomes cyanosed, the lips and tongue a deep blue, intense headache comes on, and if the blood is drawn at this stage it is chocolate colored and thick, and it may be possible to demonstrate methemoglobin. In severe cases the man may lose consciousness and the early history of American dye manufacture shows that such cases were not rare so long as processes were crudely performed, but it is not often now that poisoning is so profound. Even rarer is delirium, although instances of acute maniacal delirium are reported. In such cases the urine may

¹ R. G. Perkins, Pub. Health Rep., Washington, 1919, xxxlv, 2335.

contain hemoglobin, the pulse becomes small and rapid, respirations rapid and shallow, death may occur preceded by convulsions, or there may be coma lasting for twenty-four hours and followed by slow recovery, with weakness, exhaustion, and obstinate anemia. The nitro compounds cause more prostration than the amido and restoration to health is slower.

Chronic poisoning may give rise to polycythemia with a low hemoglobin or to a loss of red corpuscles and a polymorpholeukopenia with lymphocytosis (Malden¹). Serious lesions of the central nervous system, and especially the optic nerve, have been reported from Germany among the men exposed to dinitrobenzene which was used in great quantities as an explosive during the war.² In spite of the fact that these compounds have a severe toxic action on the blood and on the central nervous system, it is their effect on the skin that is most dreaded by the employer. Many of them, especially the phenylenediamins and the nitranilins and dinitrochlorbenzene, are excessively irritating to the skin and conjunctiva, and the eczemas which they provoke really cause more lasting disability among the workmen than does the more serious systemic poisoning.

Metol is the trade name for monomethyl para-amido metacresol sulphate which is used by photographers. It produces a trade dermatitis, inflammation of the eyelids, and in susceptible persons irritation of throat and nasal passages and bronchial irritation. Karasek in 1910 examined 40 photographic studios in Chicago for the Illinois Occupational Disease Commission, and found 8 cases of throat and bronchial irritation and 31 cases of erythematous rash of the hands and arms, occasionally involving other parts of the body and giving rise to ulcers.

Turpentine, an old industrial poison described by Ramazzini in the 17th century, has lately come into renewed prominence, especially in England, where there is a tendency to ascribe much of the illness of house painters to fumes of turpentine rather than to the white lead.³ Porrini⁴ examined 234 interior house painters and ship and submarine painters. Twenty-seven out of 89 of the former and 106 out of 145 of the latter had symptoms of turpentine poisoning. He describes a mild form consisting in irritation of the conjunctiva, nose, throat and larynx, and headache, and a severe form, with mental confusion, dizziness, sense of intoxication which may improve in the open air or grow worse, strangury, and a characteristic odor of the urine.

Lehmann⁵ believes it is not absorbed through the skin. Experimenting with dogs he found that discomfort begins at 6 mg. of turpentine per liter of air for dogs, but cats are uncomfortable at 1.17 mg., and at 6 mg. they stagger and fall unconscious, and recover, with partial loss of motion. Industrially, very little attention has been paid to turpentine till lately in England. The Illinois Occupational Disease Com-

¹ W. Malden, *Jour. Hyg.*, 1907, xii, 672.

² A. H. Hubner, *Deut. med. Wehnschrift*, 1919, xlv, 1273.

³ T. Oliver, *Brit. Med. Jour.*, 1921, 11, 100.

⁴ Porrini, *Gazz. d. Osped. d. Milano*, 1913, xxxiv, 823.

⁵ K. B. Lehmann, *Arch. f. Hyg.*, 1914, lxxxiii, 239.

mission (Hayhurst, Nicholl, and Flynn) examined 62 painters and varnishers exposed to turpentine vapors, only 14 of them being less than thirty years of age. Nearly all claimed to have suffered from headache, dizziness, roaring in the ears, inflammation of the eyes, and irritation of the throat, with cough. But the symptom most frequently noted was an increased desire to urinate, with a passage of only small amounts of urine, often with much pain and burning, and a change in the color of the urine and in the odor. Fifty-four of the 62 men described urinary symptoms, and 18 had been under treatment by physicians for bladder or kidney trouble. Twenty-one complained of inflammation of the eye, 14 of respiratory symptoms, and 7 of some form of dermatitis. Urine analysis was made in 44 and 14 showed evidence of organic kidney disease.

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FOOD POISONING AND FOOD-BORNE INFECTIONS

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THE term "food poisoning" has been and is still broadly used for illness, usually with gastro-intestinal symptoms, occurring within a few hours after eating. It is not surprising that sicknesses due to quite diverse causes have been included under this head. As popularly used, the expression food poisoning is so vague and general as to have little value for diagnostic or even descriptive purposes.

One of the facts that has emerged from food poisoning studies in the last few decades is that some of the cases formerly regarded as due to the presence of a formed poison or "ptomain" in the food are really due to the invasion of the body by micro-organisms, and are therefore to be regarded as food-borne infections rather than food poisoning.¹

Poisoning from food may be due to injurious chemical or bacterial ingredients of the food itself or to some unusual or peculiar condition in the person consuming the food. In the latter category belong the cases of food sensitization or idiosyncrasy to egg albumin or other protein substances.

Alimentary Anaphylaxis or Food Sensitization.—Coues² has described a rather typical case in a child twenty-one months old and apparently healthy except for some eczema. When the child was slightly over a year old egg white was given to it, and nausea and vomiting immediately followed. About eight months later another feeding with egg white was followed by sneezing and all the symptoms of an acute coryza. Extensive urticaria covering most of the body also appeared, and the eyelids became edematous. The temperature remained normal and there was no marked prostration. The symptoms of such attacks vary considerably in different individuals, but usually include pronounced urticaria along with nausea, vomiting, and diarrhea. The rapidity with which the symptoms appear after eating is highly characteristic. Such cases of idiosyncrasy to foods apparently fall under the head of anaphylaxis or sensitization of the organism to foreign proteins.³ Schloss⁴ has reported a case of an eight-year-old boy who showed marked idiosyncrasy to eggs, almonds, and oatmeal. Ex-

¹ A fuller discussion of the nature and variety of illnesses following the use of food will be found in Food Poisoning, Edwin O. Jordan, Chicago, 1917; Food Poisoning and Food Infections, William G. Savage, Cambridge, England, 1920.

² Boston Med. and Surg. Jour., 1912, 167, 216.

³ Allergie and Anaphylaxis, Doerr, Kolle and Wassermann's Handbuch, 2d ed., 1913, ii, 947.

⁴ Amer. Jour. Obstet., New York, 1912, 65, 731.

periments in this instance showed that a reaction was produced only by the proteins of these several foods and that extracts and preparations free from protein were entirely inert. It was further found that by injection of the patient's blood-serum, guinea-pigs could be passively sensitized against the substances in question thus showing the condition to be really one of anaphylaxis.

Skin affections in adults are apparently sometimes due to protein sensitization, the eating of certain foods such as cabbage or banana being associated in some individuals with the occurrence of eczema.¹

It is thus true that food substances that can be eaten with impunity by most persons are more or less acutely poisonous for others. This kind of food poisoning is due primarily to the constitution of the individual rather than to the nature of the food. The severity of the attack may vary from a slight rash such as that produced in some persons by eating strawberries or other fruits to violent gastro-intestinal, circulatory, and nervous disturbances.

The treatment of protein idiosyncrasy consists in the production of a condition of "anti-anaphylaxis" by systematic feeding of minute doses of the protein concerned.²

Food poisoning, due directly to some constituent of the food may depend upon the presence of: (1) Metallic or organic poison introduced by accident, negligence, or design, into food originally wholesome; (2) organic poison naturally present in the animal or plant tissues of which the food is composed; (3) pathogenic bacteria in the food; or (4) poisonous substances produced in the food by microbic activity.

1. Metallic or Organic Poisons.³—Food poisoning from the presence of the poisonous metals in food does not appear to be especially common or at all events commonly detected. Rarely such highly poisonous substances as arsenic find their way into articles of food or drink and cause extensive epidemics as in the celebrated beer-poisoning outbreak in and near Manchester, England, in 1900. In that outbreak thousands of beer-drinkers were affected, a number fatally. The source of the arsenic in the beer was found to be certain sugars used in the brewing; the sulphuric acid employed in the preparation of these sugars was discovered to contain large quantities of arsenic derived from the pyrites from which the sulphuric acid was manufactured.⁴ An outbreak of somewhat different character, although also affecting the users of alcoholic drinks, is the highly fatal outbreak of methyl alcohol poisoning, with symptoms resembling those of botulism, which occurred in a municipal institution in Berlin in 1911.⁵ In recent years methyl alcohol poisoning has become more frequent in the United States.

Lead-poisoning, due directly to lead in food or drink has been traced frequently to the use of water passing through lead pipes or standing

¹ H. Fox and J. E. Fisher, Jour. Amer. Med. Assoc., 1920, 75, 907.

² See for example, Schloss, Loc. cit.

³ See chapter on Inorganic Poisons, p. 123.

⁴ E. S. Reynolds, The Lancet, 1901, 1, 166.

⁵ Deutsch. med. Wehnschr., 1912, 38, 108; Berl. klin. Wehnschr., 1912, 49, 177, 193.

in contact with this metal. Carbonated waters in bottles with lead stoppers, or canned fruits in contact with solder or imperfectly tin-coated lead may likewise contain lead, but when used infrequently, as is generally the case, do not seem to have given rise to typical lead-poisoning. Cooking vessels lined with cheap glazes or enamels containing lead have occasionally caused lead-poisoning when used in the preparation of acid fruits. Lead carbonate is much more toxic than lead sulphate.

Tin and zinc poisoning from the use of foods that have been in contact with these metals in tin cans, zinc-lined water tanks, and the like are theoretically possible and should be kept in mind as a possibility in some cases. Actually, however, the danger from this source seems to be very slight. As regards vegetables, fruits, and the like preserved in tin cans it is especially worthy of note that tin-poisoning is apparently of rare occurrence. Lehmann¹ considers that the quantities of tin ordinarily found in canned foods possess no great hygienic significance, and his opinion is shared by most investigators. Savage states that there is no evidence "that tin plays any part of importance in connection with food poisoning acute or chronic."²

Certain individuals, however, may exhibit special susceptibility to the action of tin salts.³

Copper-poisoning.—Acute copper-poisoning from the presence of copper in food seems to be rare. Cases of poisoning due to the use of copper vessels for cooking food are very infrequent, if indeed they occur at all. Many of the instances of alleged "verdigris" poisoning reported in the older literature were probably due to other causes. The ingestion of vegetables, especially peas, to which copper salts have been added to intensify the green color, cannot, however, be regarded as devoid of danger. It has been shown that copper is retained in the body, presumably in the liver.⁴ Such retention probably results in an injurious action upon the tissues even if the effect cannot be readily traced. In the process of coloring canned peas and other vegetables it may happen that an excess of copper is added. "Much of the coppering seems to be carelessly done, and it is possible to add several hundred milligrams per kilogram to peas" (Long). Such excess may be pronounced certainly injurious.

2. Poisons Present in Normal Animal or Plant Tissue.—Some animal and plant tissues normally contain substances highly poisonous to man, and while they cannot be properly classed as foods yet they are not infrequently eaten through mistake or ignorance. The deadly poisonous mushroom is a familiar example.⁵ Fatal cases of oxalic acid poisoning due to eating rhubarb leaves have been reported.⁶ Sackett⁷

¹ Lehmann, *Arch. f. Hyg.*, 1902, 45, 88.

² W. G. Savage, *Food Poisoning and Food Infections*, Cambridge, 1920, 201.

³ See for example, Friedmann (*Ztschr. f. Hyg.*, 1913, 75, 55), who records a case where canned asparagus gave rise to poisoning apparently due to the tin in solution.

⁴ Report of the Referee Board, U. S. Dept. of Agri., No. 97, 1913.

⁵ See section on Poisonous Mushrooms.

⁶ *Jour. Amer. Med. Assoc.*, 1919, 73, 627.

⁷ *Journal of Infectious Diseases*, 1919, 24, 231.

has shown that the white snake root (*Eupatorium urticæfolium*) contains an active poisonous principle which is perhaps responsible for the curious disease of cattle in parts of the United States known as "trembles" and for the concurrent disease of "milk-sickness" in man. Certain fish, especially some species belonging to the Tetrodontidæ (puffers, balloon-fish) likewise cause acute, often fatal, poisoning when eaten either in a cooked or raw condition. In Japan, China, and the South Seas illness and death from eating such poisonous fish have frequently been recorded.¹ In some fish the flesh and eggs (roe), usually innocuous, are said to become poisonous during the spawning season. Some cases of fish-poisoning earlier attributed to natural poisonous qualities in the flesh of species commonly used as food would undoubtedly, had modern methods of investigation been applicable, have been traced to bacteria or their products.

3. Pathogenic Bacteria and Other Organisms.—The presence of pathogenic micro-organisms in the food seems to be the factor most commonly responsible for the large explosive outbreaks (Massenerkrankungen) of characteristic food poisoning. In recent years the great majority of severe food poisoning epidemics which have been carefully investigated have been traced to infection with bacteria present in or upon the food at the time of its consumption.

A noteworthy number of instances are on record of the causation of a disease so well known as typhoid fever through the eating of food contaminated with the typhoid bacillus. Bread,² sausage,³ oysters,⁴ and other food substances are known to have been the means of conveying this definite disease.

Tuberculosis likewise may be caused by the ingestion of milk containing bovine tubercle bacilli and, though much more rarely, by that of meat.

The outbreaks usually classed under the head of food poisoning, however, are due more frequently to infection with bacilli closely related to, but not identical with, the typhoid bacillus. Much confusion has surrounded the origin and chief causal factors of these outbreaks and all uncertainty cannot yet be said to be removed. A few significant facts seem clearly established: (1) The majority of the recorded food poisoning outbreaks are associated with the use of meat, fish, or other protein foods. Vegetables and cereals have been less commonly incriminated, fruits rarely. (2) Uncooked or "warmed-over" food is more frequently responsible than freshly cooked food. In many outbreaks those eating the incriminated food substance raw or imperfectly cooked are exclusively or most seriously affected, while those partaking of the same food after cooking remain exempt. (3) Outbreaks of meat-poisoning are often, though not always, connected with the use of meat from animals slaughtered while ailing ("notgeschlachtet").

¹ See for example, W. M. Kerr, U. S. Nav. Mo. Bull., 1912, 6, 401.

² K. Howell, Amer. Jour. Pub. Health, 1912, 2, 321.

³ G. Mayer, Centralbl. f. Bakt., Orig., 1910, 53, 239.

⁴ Stiles, 1912, Bull. No. 156, Bureau of Chemistry, U. S. Dept. of Agriculture.

The symptoms associated with the commoner forms of meat-poisoning are various, but usually take the form of more or less severe and sudden gastro-intestinal disturbance (nausea, vomiting, diarrhea) accompanied by fever, headache, and other manifestations. Not infrequently the gastro-intestinal symptoms are very violent and may resemble those of Asiatic cholera. The period elapsing between the ingestion of the food and the first appearance of the symptoms is usually very brief (two to twelve hours) but may be as long as twenty-four to thirty hours. Relapses sometimes occur.

Beef, veal, and ham, pork or bacon are the meats whose use is apparently most likely to give rise to meat-poisoning. Fowls have been much less commonly suspected, mutton very rarely. Sausage and chopped meat (Hackfleisch) have a disproportionately large number of outbreaks to their credit.

The bacteriology of meat-poisoning is complicated and in some respects puzzling. The first important discovery in this field is due to Gärtner¹ as the result of his investigation of a food epidemic in the town of Frankenhausen in 1888. The outbreak was traced to the use of meat from a cow which had been slaughtered because she was ill with a severe enteritis. Fifty-eight persons were affected; one of them who had eaten 800 gm. of raw meat died. Gärtner isolated from the spleen of the fatal case and also from the flesh and intestines of the cow a bacillus which he named *Bacillus enteritidis*. Animal experiments showed it to be pathogenic for many animals. Similar bacilli have been isolated in a number of other meat-poisoning epidemics, as in that at Moorseele, Belgium, in 1891, which was studied by van Ermengen.²

The meat-poisoning bacilli of this type have been found by subsequent investigation to be of two kinds. Both belong to the "intermediate" division of the colon-typhoid group. They are actively motile and in general are morphologically indistinguishable from the typhoid bacillus. Growth occurs readily on all the ordinary culture media and in most media there is no constant divergence from the characters shown by the typhoid bacillus. The "intermediate" bacilli like the typhoid bacilli produce no indol. One cultural reaction, however, stamps the members of the "intermediate" division as surely different from the typhoid bacillus, namely, their ability to ferment glucose with gas production. In this respect the meat-poisoning bacilli resemble *Bacillus coli*, but from all colon bacilli they are again distinguished by their inability to ferment lactose. Milk cultures are an important aid in diagnosis, since most organisms belonging to this division produce alkali which more or less rapidly dissolves the casein, rendering the medium translucent. The addition of litmus to the milk enables the gradual increase of alkalinity after the slight initial acidification to be readily followed.

The special media employed in the isolation of the typhoid bacillus are equally useful in the isolation of the intermediate types. Upon

¹ Breslauer ärztl. Ztg., 1888, 10, 249.

² Bull. de l'Acad. Royale de méd. de Belgique, 1892, 1025.

the Endo medium, Löffler's malachite green medium (considered by many workers especially favorable for these organisms), the Conradi-Drigalski agar, and some other media the bacilli in question grow well and characteristically. The colonies resemble those of the typhoid bacillus in all cases so that further tests are necessary for identification. The two kinds of meat-poisoning bacilli above referred to resemble one another in all morphologic and cultural characters. Agglutination alone enables, or forces, a differentiation to be made.

Organisms like those first isolated by Gärtner, *Bacillus enteritidis*, have been found in a number of meat-poisoning outbreaks, those of Moorseele,¹ Ghent,² and St. Johann³ being among the most important or best studied cases. Mayer⁴ has compiled a list of 48 meat-poisoning outbreaks occurring between 1888 and 1911, and attributed to *B. enteritidis*, Gärtner. These outbreaks involved about 2000 cases and 20 deaths. In 23 of the 48 outbreaks the meat implicated came from animals known to be ill at the time or shortly before they were slaughtered. In addition, sausage and chopped meat were responsible for 11 outbreaks. Two *B. enteritidis* outbreaks were attributed to "Vanillepudding," 1 to potato salad.

The outbreaks of gastro-enteritis due to the other type of bacillus are clinically and epidemiologically similar to those caused by *Bacillus enteritidis*. The reason for distinction lies in the fact that the bacilli found in these cases refuse to agglutinate with the Gärtner bacillus serum, while they do give completely reciprocal agglutinative reactions with the so-called paratyphoid bacilli of the variety *B. suispestifer* or *B. paratyphosus*. The epidemics at Breslau,⁵ Aertryck,⁶ Belgium, Hatton,⁷ England, and Düsseldorf⁸ are often-quoted examples of food poisoning traced to this bacillus. German investigators as a rule regard such "paratyphoid" bacilli as identical with *B. suispestifer*, but Bainbridge⁹ and other English writers distinguish between *B. suispestifer* and *B. paratyphosus*. To the former are attributed the food poisoning outbreaks here referred to, while the name *B. paratyphosus* is reserved for those bacilli causing an illness "clinically indistinguishable from enteric fever." Mayer¹⁰ gives a list of 77 food poisoning outbreaks occurring from 1893 to 1911 with about 2000 cases and 20 deaths which were ascribed to this organism. According to Mayer's tabulations the meat from ailing animals is responsible in a much smaller proportion of cases (10 in 77) than in the *B. enteritidis* outbreaks (23 in 48). Sausage and chopped meat gave rise to 18 outbreaks. The

¹ Van Ermengem, Bull. de l'Acad. Royale de méd. de Belgique, 1892, 1025.

² Van Ermengem, Die pathog. Bakterien der Fleischvergiftungen, Kollé und Wassermann Handbuch, 1903, ii.

³ Rimpau, Klin. Jahrb., 1910, 30.

⁴ Dtsch. Viertelsjahreschr. f. Öffentl. Ges., 1913, 45, 58-59.

⁵ Kaensche, Ztschr. f. Hyg., 23, 53.

⁶ De Nobele (see Van Ermengem, Kollé und Wassermann Handbuch, 1903, 2, 637.

⁷ Durham, Brit. Med. Jour., 1898.

⁸ Trautmann, Ztschr. f. Hyg., 1903, 44, 139.

⁹ Lancet, March 30, 1912, 849.

¹⁰ Dtsch. Vierteljahrsschr., 1913, 45, 60-62.

proportion of foods other than meat, mostly those containing milk or eggs, is notably larger in the *B. suipestifer* list.

On the basis of these facts some authors are inclined to make a rather sharp distinction between cases of food poisoning caused by the flesh of diseased animals that have been killed while ailing ("Not-geschlachtet" to use the expressive German term), and cases due to contamination of the meat, or other food substance, during transportation or preparation.¹ The apparently greater preponderance of the *Bacillus enteritidis* type in the former class of cases, *B. suipestifer* or *B. paratyphosus B* in the latter favors this view.

Bearing directly on this question is the discussion concerning the distribution of the food poisoning bacilli in nature. Most investigators in Germany, where the majority of food poisoning outbreaks have occurred, or have at least been bacteriologically studied, are of the opinion that *Bacillus suipestifer* (the same in their opinion as *B. paratyphosus B*) is much more widely distributed than *B. enteritidis* and that it occurs, especially in certain regions, as in the southern part of the German Empire, quite commonly in the intestinal tract of healthy human beings. These paratyphoid carriers, it is supposed, may contaminate food through handling or preparation just as typhoid carriers are known to do. A number of outbreaks in which such contamination of food during preparation is thought to have occurred have been reported by Jacobitz and Kayser² (vermicelli), Reinhold³ (fish), and others. Reinhold notes that in one outbreak several persons who had nursed those who were ill became ill themselves, indicating possible contact infection. In another outbreak also reported by Reinhold it was observed that those who partook of the infected food (dried codfish) on the first day were not so severely affected as those who ate what was left over on the second day. A bacillus belonging to the paratyphoid group was isolated from the stools, but not from the dried codfish. These facts were interpreted as signifying that the fish had become infected in the process of preparation and that the bacilli multiplied in the food while it was standing.

There seems no doubt that certain cases of food poisoning are caused by contamination of the food during preparation and are sometimes at least due to infection by human carriers. The bacilli in such cases are usually (many German investigators) or always (most English bacteriologists) of the *Bacillus paratyphosus* or *B. suipestifer* type. Other cases are due to pathogenic bacteria derived from diseased animals and these bacteria are often of a slightly different character (*B. enteritidis*, Gärtner). It is still unsettled whether both types of food poisoning bacteria are always associated with disease processes of man or animals, or whether they are saprophytic organisms of wide distribution which may at times acquire pathogenic properties. In certain regions, as in Northern Germany and England, such bacteria are rarely if ever found

¹ See for example, M. Müller, Centralbl. f. Bakt., Orig., 1912, 66, 222.

² Centralbl. f. Bakt., I Orig., 1910, 53, 377.

³ Cor.-Bl. d. Schweiz-Aerzte, 1912, 42, 281, 332.

except in connection with definite cases of disease. In parts of South-western Germany, on the other hand, they are said to occur with extraordinary frequency in the intestines of healthy men and animals. Savage¹ believes that some confusion on this subject exists owing to the existence of saprophytic bacteria which he calls "Paragärtner" forms and which bear a close resemblance to the "true" Gärtner bacilli. They can be distinguished from the latter only by an extended series of tests. The bacilli of this group show remarkable variability, and in the opinion of some investigators "mutations" sometimes occur which lead to the transformation of one type into another.² Further investigation is needed along these lines.

A powerful toxin (endotoxin) is produced by some bacteria of the paratyphoid and enteritidis types, and since this is heat-resistant to a considerable degree some cases of food poisoning with "cooked" food have been thought to be due to intoxication with bacterial products rather than to a true infection. It is difficult, however, to be sure that such cases actually occur. As has been stated, food is undoubtedly sometimes infected during preparation or service after it has been cooked. The ordinary processes of "cooking," moreover, do not ensure bacterial sterility. Living bacilli of the enteritis group have, in fact, been isolated from the stools of persons poisoned by cooked foods. While the possibility of intoxication with the products of these bacteria must be reckoned with, actual proof of such intoxication is not yet forthcoming.

Food Poisoning from *Bacillus Proteus* (?).—In a number of food poisoning outbreaks bacilli belonging to the proteus group of Hauser³ have been found in the incriminated food and the bodies of affected persons, and these bacilli have been held to be responsible. The outbreak described by Pfuhl⁴ is typical. Eighty-one soldiers in the garrison at Hannover were suddenly attacked with acute gastro-enteritis four to twelve hours after eating sausage meat. The meat seemed to have been prepared with ordinary care and was quite normal in appearance, taste, and smell. *B. proteus*, however, was found in large numbers in the sausage. Rats and mice fed with the sausage became ill and *B. proteus* was isolated from the blood and internal organs. Since these animals sometimes die when fed with normal meat, and since *B. proteus* and other common intestinal organisms are often isolated from the body after death, such evidence is not convincing. The human cases do not appear to have been investigated. Other outbreaks attributed to *B. proteus* are similarly inconclusive. In none of these can it be said to be definitely established that this organism was the exciting cause, either by infection or by toxin production in the food substance.

Although not perhaps usually classed as food poisoning the serious

¹ Jour. Hyg., 1912, 12, 1.

² See Sobernheim and Seligmann, Centralbl. f. Bakt., 1911, Ref. Beihefte, 50, 000.

³ Ueber Fäulnisbakterien, Leipzig, 1885.

⁴ Ztschr. f. Hyg., 1900, 35, 263.

disease **trichinosis** should here be mentioned. As well known this disease in man is due to the ingestion of meat, practically always that of swine, which contains the encysted stage of a reniform worm, *Trichinella spiralis*. The cysts are dissolved in the alimentary tract by the digestive juice and the liberated worms, male and female, become sexually mature in the intestine within two or three days. In five or six days more the female gives birth to 8000 to 10,000 embryos which pierce the intestinal wall and may be carried by the blood-stream to remote parts of the body. The muscular tissue in various regions is then invaded by the young worms, and serious, often fatal, injury results. The case mortality has been as high as 30 per cent. in some epidemics. In Germany from 1889 to July 31, 1912, there were 659 cases of trichinosis and 34 deaths, so that in point of fatality this form of infection has outranked most other forms of meat-poisoning.¹ Fortunately the knowledge that the encysted worms are killed by thoroughly cooking the meat, aided possibly by some improvement in methods of inspecting the bodies of freshly slaughtered hogs, has greatly reduced the danger from this source. The mischievous custom of eating raw or partially cooked pork, which prevails, especially in certain parts of Germany, is at the bottom of the trouble. Inspection is at best an expensive and uncertain way of lessening a danger which can be altogether avoided by refraining from the use of raw pork.

In the same category with trichinosis must be put **teniasis** or infection with various cestode worms, the so-called tape-worms. As well known the adult worm—in this country usually *Tenia saginata*—inhabits the intestines while the larval worm (*Tenia solium*) may invade the tissues and become encysted in various organs (cysticercosis). Meat—the flesh of swine or beef—infected with the encysted worms is the means by which these parasites are introduced into the human body. “Measly pork” and beef can be detected by a proper system of meat inspection. Thorough cooking does away with all danger from this source.

4. Poisonous Products of Bacteria and Other Organisms.—Poisonous products of bacteria and other micro-organisms have in the past been held responsible for a great many isolated cases and extensive epidemics of food poisoning. It seems probable, however, that the frequency of direct toxic action as compared with that of infection has been considerably exaggerated.

The best known example of poisoning by means of bacterial products is the rare disease **botulism**. The name botulism, first applied to sausage poisoning (Lat. *botulus*=sausage) in general, has come to have a more restricted meaning and is now properly used for the form of intoxication due to the products of a specific micro-organism, *Bacillus botulinus* (*Clostridium botulinum*). In 1885 Van Ermengen² discovered a peculiar bacillus in the uneaten portion of a ham which had poisoned 50 persons and caused 3 deaths. Other portions of the animal from which this ham

¹ Mayer (after Böhm), Deutsch. Vierteljahrsschr. f. Öffentl. Ges., 1913, 45, 44.

² Ztschr. f. Hyg., 1897, 26, 1.

was derived had been eaten without producing any ill effects, and the significant observation was made that the incriminated ham had been kept in the same cask with the non-poisonous ham, but had been under anaërobic conditions. The powerfully toxic anaërobic bacillus isolated from the ham and named by Van Ermengen *B. botulinus* has since been found in other outbreaks of the same character. Mayer¹ has tabulated 21 instances of botulism recorded in Europe since 1886.² Including earlier epidemics probably to be referred to this cause the total number of cases in European outbreaks amounts to about 800, and of deaths to 200. All observers are agreed that the case mortality in botulism is much higher than in paratyphoid poisoning.

The symptoms of botulism are different from those of paratyphoid meat-poisoning. An intense toxic action upon the nervous system is especially characteristic. The onset is slower, the first symptoms not appearing until about twelve to twenty-four hours after the meal. Constipation is common. Nausea, gastric pain, and diarrhea are frequently absent, but may occur. There are invariably visual disturbances, such as dilation of the pupils and double vision, and difficulty in swallowing and in speaking are usual. The central nervous system, in general, is profoundly affected, exhaustion is great, and recovery is greatly prolonged. The pulse is sometimes small and rapid, sometimes slow. Consciousness is not impaired. The temperature is usually subnormal, but may be high. There is progressive loss of muscular action, death usually resulting from respiratory failure. Several observers have noted anatomic changes in the spinal cord and medulla, such as numerous hemorrhages and histologic alterations of the ganglion cells corresponding to the clinical signs of nervous disturbance. Further study is necessary to determine the physiologic action of the toxin and the lesions produced by it.

Bacillus botulinus is a rather large, spore-bearing, anaërobic bacillus which can be cultivated anaërobically on the usual glucose media. Some experienced students of this organism regard the type of colony formation as highly characteristic. Early observers believed that growth occurred best at about 20° C. and hardly at all at 37° C., but later experiments have shown that a good growth is obtained at 37° C. as well as at lower temperatures. There is no convincing evidence that infection in man follows the ingestion of this organism or its spores. The dangerous character of *B. botulinus* is apparently solely due to the powerful toxin that is produced in food-stuffs outside the body. The poison is a true bacterial toxin resembling in many respects the toxin produced by diphtheria and tetanus bacilli. It is quickly destroyed by boiling.

Great advances have been made in our knowledge of botulism in recent years, largely through the work of Dickson, Meyer, Geiger, and their associates.³

¹ Op. cit., p. 57.

² See also Schumacher, Münch. med. Wchnschr., 1913, p. 124.

³ E. C. Dickson, Botulism, Monograph No. 8 of the Rockefeller Institute for Medical Research, 1918.

It has been shown that this form of food poisoning has occurred in man and certain domestic animals (fowls, limberneck; horses and cattle, forage poisoning) in various parts of the United States, notably on the Pacific Coast. The recorded outbreaks have increased considerably in number during the past few years, but whether this represents an actual increase in occurrence is not altogether clear. Between 1900 and 1921, 39 human outbreaks were recorded in California alone, with a probable total of 130 cases and a mortality of about 72 per cent. No class of preserved foods is altogether exempt. String beans, asparagus, sweet corn, beets, spinach, ripe olives, fruit, and cheese have all been implicated in outbreaks of botulism.

Foods canned in the home and less frequently those prepared commercially on a large scale have caused botulism-poisoning.

It is evident that the high heat resistance of the spores of *Bacillus botulinus* and their ability to germinate, multiply, and produce their toxin at moderate temperatures are the factors primarily responsible for this dangerous form of food poisoning. The spores resist the temperature of boiling water for several hours and must be exposed to steam under pressure to insure their destruction. The exact thermal death point depends upon the reaction of the medium and other factors, but, in general, it may be said that a temperature of at least 230° F. (110° C) must be maintained for forty minutes in order to kill all spores.

Observations now in progress indicate that *Bacillus botulinus* is widely distributed in nature. It has been found on cherries and olives on the tree, on the leaves of plants; in moldy hay, and in hog manure. It has also been found in samples of soil in widely separated parts of North America and Europe. Important observations on the relation of *B. botulinus* to forage-poisoning in horses and cattle have been made by Graham¹ and others.

Two types of *Bacillus botulinus* have been found in the United States. They are alike culturally, but are entirely distinct in their immunologic relations. Specific antitoxins can be produced for the two types of *B. botulinus* (designated as Type A and Type B) by the same methods as those used for the production of diphtheria antitoxin. In animal experiments the antitoxin exerts considerable therapeutic effect, but in human botulism outbreaks little success has so far been obtained by the administration of botulism antitoxin. This may be due partly to the fact that antitoxin prepared from the B strain has no effect in neutralizing the A toxin, and, conversely, partly to the failure to use antitoxin until too late in the course of the disease.

Ergot-poisoning, or ergotism, was relatively common in Europe in earlier times. Many extensive outbreaks were reported during the 17th, 18th, and first half of the 19th centuries. The cause is the poisonous substance or ergot produced in rye and other grains by the growth of a parasitic fungus, *Claviceps purpurea*. In times of famine when spoiled grain was perforce used in many districts the loss of life from

¹ Jour. Bact., 1921, 6, 69.

ergot-poisoning was often terrible. Better facilities for the transportation of wholesome grain into regions where crops have failed, and improved methods of sorting out the diseased grain from the healthy have greatly reduced the frequency of this form of food poisoning.

Vetch-poisoning, or lathyrism, is a disease observed in parts of Southern Europe and elsewhere and is connected with an exclusive or almost exclusive diet on the chick pea or pulse (*Lathyrus*). Nervous symptoms predominate. The disease seems of a relatively mild type and recovery often occurs. Practically nothing is known about the cause.

Pellagra, now known to be widely spread in this country as well as in Europe, has been attributed by many observers to the ingestion of poisonous substances present in spoiled Indian corn or maize. The weight of evidence, however, indicates that pellagra, like beriberi, scurvy, and rickets, is a deficiency disease due to dietary inadequacy.

Spoiled and Decomposed Foods.—Foods of various kinds which have been more or less decomposed by bacterial activity are not necessarily poisonous and are, in fact, eaten by preference and without injury by many persons. "High" game, well "ripened" cheese, and even in some countries eggs after long burial in the earth are often consumed without any noticeable bad effects.

It must be admitted that the amount of harm caused by the products of ordinary bacterial decomposition is still largely conjectural. In fact, the recorded outbreaks of "poisoning" due to eating definitely decomposed food seem to be less numerous than those in which the responsible article of food has been fairly fresh or well preserved. One of the most experienced students of food poisoning, W. G. Savage, concludes a recent study upon the alleged toxicity of putrid food with the statement: "A study of the evidence along these accessory lines of inquiry singularly fails to bring forward any evidence associating the consumption of food in a state of incipient putrefaction with illness in those who consume it."¹

At one time cases of "ptomain-poisoning" were commonly attributed to the use of decomposed food. The term **ptomain** has been applied to the alkaloid-like substances formed when proteins are subjected to putrefaction. "They include a large number of substances of the fatty series, amines, and members of the pyridin and chinolin series. In addition there are a number of bases, some belonging to the pyridin group, others yielding reactions of chinolin, while still others resemble muscarin" (Taylor). The great majority of the ptomains are innocuous, but certain of them possess marked poisonous properties. Perhaps those best known in connection with food poisoning outbreaks are *tyrotoxin*, first obtained by Vaughan from cheese, and *mytilotoxin*, isolated by Brieger from poisonous mussels. The conditions under which such substances are produced are not known. Possibly particular bacterial species are concerned in the generation of poisonous ptomains. Vaughan and McClymonds, however, have reported finding toxicogenic

¹ Jour. of Hygiene, 1921, 20, 69.

bacteria in practically all cheese,¹ though in general, cheese seems to be a wholesome article of diet.²

There can be little doubt that the term "ptomain-poisoning" is an inappropriate one with respect to the great mass of cases ordinarily imperfectly diagnosed and lumped together under this head. The more carefully investigated food poisoning outbreaks of the past few years have been traced in the majority of instances to infection with some member of the *Bacillus paratyphosus* or *B. enteritidis* group, or to poisoning with the toxin of *B. botulinus*, and the putative cases of "ptomain-poisoning" have correspondingly shrunk in number. The term should probably be discarded altogether.

Treatment and Prevention.—Little can be said about methods of treatment beyond the obvious suggestion that they must be adapted to individual conditions. If sufficiently early treatment is possible the alimentary tract should be freed from its deleterious contents; if poisonous substances have entered the circulation, saline infusion hypodermically or intravenously will aid in their elimination.

In the United States the most serious form of food poisoning that has been adequately studied is botulism, and the treatment of this disease has not passed the experimental stage. There are at least two distinct strains of *Bacillus botulinus*, Type A and Type B, and each strain produces its own toxin not neutralizable by the antitoxin of the other type. Whether for this reason or because of other factors, the antitoxin treatment has not been very successful in the practical treatment of developed botulism cases. The greatest likelihood of success will exist when an antitoxin serum prepared from both Type A and Type B is available, and when such antitoxin is administered at about the time the first symptoms appear or, as may sometimes be possible, earlier.

It is plain from the foregoing discussion that the surest method of preventing those forms of food poisoning caused by the paratyphoid-enteritidis group is to use only food that has been thoroughly cooked and that, after cooking, has been kept clean, and has been handled during preparation and serving by healthy persons. In the case of meat care should be taken also that it is derived only from healthy animals.

The prevention of botulism has received particular attention in consequence of the relatively large number of outbreaks in the United States since 1910. Since this disease is due to the use of imperfectly preserved food, the obvious method of prevention would seem the application of sufficient heat to surely destroy all *botulinus* spores. This, however, is not always easy to carry out in practice. In rural districts much food is canned in the household where equipment for using steam under pressure is frequently not available. It is significant that domestically canned food has caused a disproportionately large amount of botulism. In the larger commercial establishments where

¹ Tr. Assoc. Amer. Physicians, Philadelphia, 1898, 13, p. 266.

² Langworthy and Hunt, Farmers' Bull. 487, U. S. Dept. of Agri., 1912.

proper apparatus is at hand, it is still desirable not to impair the quality of certain foods by overheating, and the natural tendency is to use a temperature sufficient to insure safety and prevent spoiling, but no more. Unequal degrees of heat penetration in different foods and in different "packs" of the same food introduce an element of uncertainty difficult to gage. Intensive investigation of the botulism problem under the auspices of the National Cannery Association is in progress.

The individual consumer has one method of protection against botulism that deserves wide publicity. Since the botulism toxin is readily destroyed by boiling, the thorough heating of canned food as soon as removed from the container constitutes a very effective safeguard. "Home-canned" foods especially, should be uniformly subjected to thorough reheating before being served.

Many observers have reported that the particular samples of food implicated in botulism-poisoning show signs of spoiling, and possess a characteristic odor which should serve as a warning signal. It does not seem safe to assume, however, that unmistakable signs of spoiling are always present in foods containing the botulism toxin. In fact some instances are on record where the existence of unusual taste or odor has been specifically denied by those who had eaten the toxin-containing food.

Under no circumstances should apparently spoiled food be tasted to determine whether it is really edible. Botulism toxin is so powerful that in several instances the mere essay of tasting spoiled or soured canned food has resulted fatally.

The Examination of Suspected Food.—Simple inspection or physical examination of food cannot as a rule be relied on to show its wholesomeness. Meat that has passed veterinary inspection has been the cause of several European outbreaks. Bainbridge¹ cites an instance where sausages had apparently given rise to symptoms of meat-poisoning. The inspector of the slaughter-house did not believe in this explanation and in order to demonstrate the harmless nature of the sausages consumed a considerable quantity of them. Within a few hours he was seized with acute gastro-enteritis and died; *Bacillus enteritidis* was isolated from his organs and from the sausage.

Suspected food, without any addition of chemical preservatives, should be placed on ice until the examination is commenced, which should be as soon as possible. Suitable portions should be macerated in sterile physiologic salt solution and a bacterial examination made with special reference to the presence of members of the paratyphoid group. It must be remembered, however, that bacilli with the cultural characters of these organisms are not uncommon in nature and that carefully controlled agglutination tests must be carried out, including where possible tests with the patient's own serum. Hand in hand with such examinations should go the bacterial examination of the blood and secretions of the patient.

Mice have been often used for feeding experiments with suspected

¹ The Lancet, March 30, 1912.

meat, but they are not suitable for this purpose since they frequently succumb when fed with perfectly fresh and uninfected meat.¹ Animal experiments are further complicated by the fact that bacilli of the paratyphoid-enteritidis group are frequently found in the bodies of normal rats, mice, guinea-pigs, and other animals. Bacterial findings of this sort after inoculation or feeding of suspected material must hence be interpreted with caution.

Material suspected of containing botulism toxin should be injected into mice or guinea-pigs. The symptoms of true botulism-poisoning are highly characteristic and hardly to be mistaken for anything else. If time and experience permit, the isolation of *Bacillus botulinus* may be undertaken, but the finding of this organism hardly adds to the force of the demonstration that the formed toxin was present in the suspected food.

Chemical examination of the foods implicated in such poisoning outbreaks as those here considered has rarely given significant results. As elsewhere pointed out examination for ptomaines is of little value, and the same may be said of attempts to discover evidence of putrefactive changes. Smell and appearance are usually fully as significant as chemical changes due to decomposition. Examination for poisonous metals and preservatives is carried out by the usual qualitative methods but needs experience in food chemistry.

¹ See for example, Schellhorn, *Centralbl. f. Bakt. I Orig.*, 1910, 54, 428.

POISONOUS MUSHROOMS

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BALTIMORE, MD.

INTRODUCTION

FROM primitive times, when members of the human family depended for sustenance upon the flesh of animals and upon the wild plants which grow in meadow and forest, the fungi have been collected and eaten in many countries. In certain areas, indeed, the edible fungi or, as they are usually called, the mushrooms have been highly prized for the table, and so complete was the knowledge of their botanic and dietetic properties that they early found their way to the public markets for the sale of food as these were installed in the growing towns and cities. According to Paulet,¹ from time immemorial mushrooms have been sold, especially during Mid-Lent, in the public markets of Pekin, Petrograd (St. Petersburg), in Florence, and in the smaller cities and towns of Hungary, and of Tuscany in Italy. The ancient Babylonians and the early Romans employed mushrooms in great quantity both as delicacies for the tables of the rich and as a staple article of diet for the poorer classes. In consequence of this wide use of mushrooms occasioned not only by the poverty of the indigent, who were forced to utilize any plants which would on experience prove to have nutritive properties, but also by the delicious taste and flavor of the more abundant common species, knowledge of the properties of mushrooms became general and the peasants of many European countries exhibit a profound acquaintance with mushrooms and an ability to distinguish the many edible and harmful species which is no less surprising today than it was in the time of Paulet. Add to this the fact that all the mushrooms grow wild and can be had for the labor of collecting and that they are among our most beautiful plants, and we are in a position to understand their appeal to collectors the world over. Indeed, the wild mushrooms which at certain seasons of the year are really abundant in well-watered fields possess a delicacy of flavor which is never surpassed and seldom equalled by any of the cultivated species. The use of mushrooms for food has increased greatly in America during the past two decades, especially among our foreign-born citizens, and there are hundreds of people who give up much of their leisure time during the mushroom season to scouring the meadows and woods for this highly prized addition to our list of dietary delicacies.

POISONING BY MUSHROOMS

Very early in history, as mushrooms were used for food, cases of poisoning from them must have occurred, inasmuch as the species which were offered for sale were carefully studied for distinguishing botanic features and separated from other species which were known to be poisonous. Cases of mushroom poisoning were described centuries ago, and again, according to Paulet, the Latin historian Pliny states that deaths from mushroom-poisoning were by no means uncommon in early Rome, several deaths in the Consular families being attributed to this cause. He states that Pope Clement VII, the Emperor Jovian, the Emperor Charles VI, and Berronill of Naples, as well as the widow of the Czar Alexis all lost their lives from poisonous mushrooms. The Emperor Claudius also died shortly after eating mushrooms. There is some doubt, however, whether these mushrooms were really poisonous and substituted for the edible mushrooms usually served to the Emperor or whether the poison which caused the Emperor's death was not purposely added to his food.

Probably the earliest case of mushroom-poisoning on record is that of the family of the Greek poet Euripides, who lost his wife, two sons, and a daughter from eating poisonous species on some occasion when the poet was absent from his family.

¹ Paulet, *Traité des champignons de France*, 1793.

The first individual to study the question of mushroom-poisoning with any degree of care was Paulet in the latter part of the 18th and the early part of the 19th centuries. He was much impressed by the number of deaths from mushroom intoxication in France during his own lifetime, and states that in the period from 1749 to 1788 there were 100 deaths in the vicinity of the city of Paris alone. In modern times Palmer,¹ of Boston, recorded 33 cases, with 21 deaths; Forster,² of Charlestown, added 44 cases, with 14 fatalities; Falck,³ in Germany, reported 53 cases, with 40 deaths, and Bardy⁴ described 60 cases in the Vosges country in France. The celebrated French mycologist, Guillaud,⁵ estimated that about a hundred deaths from poisonous mushrooms occurred annually in the southwest of France.

In many other countries mushroom-poisoning is very common. Inoko⁶ in Japan in 1887 reported over 480 cases of mushroom intoxication for a period of eight years for that country, with 103 deaths. In 1900 Gillot⁷ collected over 200 cases of poisoning, most of them in France, and in 1907 the present author⁸ added 235 cases collected from the German and English literature, and from the French after 1900. Of these cases, 204 were due to our most poisonous species, *Amanita phalloides*, Bulliard. Of these, 153 died. The other 31 cases, with 22 deaths, were due to unidentified mushrooms, but the symptoms pointed to the same species. In addition, Hegi⁹ in 1900 reported 4 cases in one family, with 3 deaths, due probably again to *Amanita phalloides*.

In America as early as 1871 cases of mushroom-poisoning were described by Cheney,¹⁰ who reported 3 cases and 2 deaths from unidentified fungi. Later McGlenn¹¹ reported 6 cases of toadstool-poisoning, with 4 deaths, and Kessler¹² in 1880 observed 2 cases of poisoning, with 1 death, from eating fungi gathered on the lawn. In this report it is interesting to note that the fatal case exhibited nervous symptoms, stupor, coma, contraction of the pupils, and that Kessler, who was familiar with the work of Schmiedeberg and Koppe on muscarin, administered atropin to overcome them.

Since our last collection of cases, instances of mushroom intoxication have been reported from many different countries. Thus in France in 1909 Boyer¹³ reported 2 instances of *Amanita muscaria* intoxication involving 5 individuals. All recovered. In the first instance a cat which was fed upon the cooked fungi died with symptoms of *Amanita muscaria* poisoning. In 1912 Marcland and Forgeot¹⁴ described 3 cases in one family from unidentified mushrooms, the symptoms pointing to *Amanita muscaria*. Guéguen¹⁵ states that in the season of 1911, 9 cases occurred in Paris, with 2 deaths, 23 in Trevaux, with 9 deaths, and 2 in Lamalen des Bains, with 1 death. All these were due to *Amanita phalloides*. According to Chauvet¹⁶ Guéguen estimated the number of cases occurring annually in France at about 200 being due to *Amanita phalloides*, *Amanita verna*, *Amanita citrina*, *Amanita muscaria*, and *Amanita pantherina*. Chauvet regards all the volvaria as poisonous as well as *Lepiota helveola* (*Lepiota brunâtre*). Labesse¹⁷ states that at Trevoux in the district L'Ain in November, 1911, 39 cases of poisoning, with 9 deaths, occurred among the individuals of one party who ate unidentified mushrooms gathered by a member of the company and cooked for them in a restaurant. To these Roch and Sliva¹⁸ added 4 cases of poisoning by *Amanita citrina*, variety *mapa*, with 1 death. In 1912

¹ Palmer, Quoted by Forster in Medical Communications, Mass. Med. Soc., 1890, 15, 209.

² Forster, Boston Med. and Surg. Jour., 1890, 125, 267.

³ Falck, Handb. der. gesam. Arzneimittellehre mit Einschluss der Toxikologie. i, 12, p. 282.

⁴ Bardy, Bull. Soc. philomat. des Vosges, 1883, 84, 9.

⁵ Guillaud, Bull. Soc. Mycol. de France, 1885, i, 123.

⁶ Inoko, Mittheil. a. d. Med. Fac. d. k. Jap. Univ., Tokio, 1887-89, pp. 227-306.

⁷ Gillot, Étude médicale sur l'empoisonnement par les champignons, Lyon, 1900.

⁸ Ford, Johns Hopkins Hosp. Bull., April, 1907, xviii, No. 193, 123.

⁹ Hegi, Deutsch. Arch. f. klin. Med., 1900, 65, 385.

¹⁰ Cheney, Pacific Med. and Surg. Jour., 1871-72, v, 119-121.

¹¹ McGlenn, Med. Herald, Louisville, 1879-80, i, 255.

¹² A. Kessler, Amer. Jour. Med. Sci., October, 1880, n. s., 80, pp. 393-399.

¹³ Boyer, Jour. de Méd. de Bordeaux, 1909, p. 235.

¹⁴ Marcland and Forgeot, Limousin Med. Limoges, 1912, pp. 123-126.

¹⁵ Guéguen, Compt. rend. Soc. de Biol., 1912, lxxii, 159. See also Bull. trim. de la Soc. Mycol. de France, 1912, xxvii, 60.

¹⁶ S. Chauvet, Gaz. d. hôp., Paris, 1912, lxxxv, 1499-1504.

¹⁷ Labesse, Anjou Méd., 1912, xix, 99-116.

¹⁸ Roch and Sliva, Rev. Med. de la Suisse Rom., 1912, xxxii, 843.

Fonvielle and Charuel¹ reported 4 cases, with 1 death, and Goy² observed 5 cases, with 1 death, from *Amanita phalloides*, while Labesse³ reported over 70 deaths in France in the district known as Maine-et-Loire, in a large number of cases due to a great variety of fungi, including *Amanita phalloides*, *Amanita muscaria*, and *Entoloma lividum*. Sartory⁴ (cited from Roch) reported 249 cases of mushroom intoxication, with 105 deaths, between August 20th and September 10th in the summer of 1912. He further states that in 1912 in Alsace alone there were 89 cases, with 45 deaths, from *Amanita phalloides*, 25 victims of *Amanita citrina*, with 12 deaths, and 2 non-fatal poisonings from *Amanita verna*.

In 1913 Roch⁵ published an important thesis upon poisonous mushrooms including a large number of cases observed by himself and others. The combined statistics of Gillot, Sartory, and Roch (including some of the cases reported by the present writer) give 496 cases of *Amanita phalloides* poisoning (or its-varieties), with 261 deaths, a mortality of about 52.6 per cent. In 1913 Charuel⁶ reported 4 cases of poisoning by *Amanita phalloides*, and Sartory⁷ (quoted from Roch) in 1915 reported 66 cases of poisoning from *Entoloma lividum*, with 1 death, in France in 1912 and 26 cases in 1913 from the same species. Somewhat later in 1917 Roch⁸ in Switzerland described 100 cases of mushroom-poisoning in the neighborhood of Geneva in the summer of 1916. Of these, 8 cases, with 2 deaths, were due to *Amanita phalloides*, 9 non-fatal cases due to *Amanita muscaria*, 32 to *Entoloma lividum*, 17 due probably to *Entoloma lividum*, 7 traced to spoiled *Tricholomas*, 8 to *Russula emetica* and *Russula sardonica*, 1 fatal case to decayed *Chantarelles*, while the remainder, 18 cases, with 1 death, were due to unidentified fungi.

This gives a total of nearly 1000 cases (990), with 318 deaths, reported in the French literature. Of these, 556 were due to *Amanita phalloides*, with 262 deaths, a mortality of 47 per cent., 124 due to *Entoloma lividum*, with 1 death, 17 due to *Amanita muscaria*, with no fatalities, while the rest were due to fungi not clearly identified.

In Germany and Austria work upon mushroom-poisoning during the last few years is extensive and very valuable. Lövegren⁹ in 1909 reported 5 cases of poisoning, with 1 death, from *Hebella esculenta*, the first careful study of this condition in a number of years. In 1912 Schürer¹⁰ reported the poisoning of a family of 6 persons, parents and 4 children, of whom the youngest, a child of five years, who ate a large portion of the mushrooms, died. The symptoms pointed to intoxication by *Amanita phalloides* (Knollenblatterschwamm). In the same year Frey¹¹ described 2 fatal cases, a boy of twelve and a boy of fourteen years, who died four to five days after eating fungi thought to be some kind of russula. Both cases showed acute nephritis. Brüderle¹² in 1915 described the lesions in 2 fatal cases of *Amanita phalloides* poisoning. The following year Umber¹³ reported the poisoning of 6 individuals from morels (helvellas?), and in the same year Lyon¹⁴ described 2 instances of poisoning thought to be due to *Cantharellus aurantiacus*, the symptoms and lesions, however, suggesting helvella poisoning. Another case of morell poisoning was described by Henius¹⁵ in 1916. In 1917 Fahr¹⁶ reported a fatal case of *Amanita phalloides* intoxication with a careful microscopic examination of the internal organs, and Schultze¹⁷ added 6 cases of poisoning from the same fungus, with 5 deaths. The clinical symptoms were described very accurately and fully, the autopsies being reported later by

¹ Fonvielle and Charuel, Jour. de Practiciens, 1912, xxvi, September 28, 615.

² P. Goy, Rev. gen. de clin. et de ther., Paris, 1912, xxvi, 791.

³ Labesse, Anjou méd., 1913, xx, 276.

⁴ A. Sartory, Les empoisonnements par les champignons (été de 1912), Paris, 1912. Quoted from Roch.

⁵ M. Roch, Les empoisonnements par les champignons, Geneva, 1913.

⁶ Charuel, Arch. de med. et pharm. nav., Paris, 1913, c, 81-109.

⁷ A. Sartory, Bull. des Scien. pharm., Mars-Avril, 1915, xxii, 68.

⁸ Roch, Rev. méd. de la Suisse Rom., Geneva, 1917, xxxvii, 253-270.

⁹ Lövegren, Jahrb. f. Kinderheilk., 1909, xix, 412-421.

¹⁰ J. Schürer, Deutsch. med. Wchnschr., 1912, xxxviii, 548-551.

¹¹ W. Frey, Zeitschr. f. klin. Med., Berlin, 1912, lxxv, 455-471.

¹² Brüderle, Beitung zur Toxikologie Symptomatologie und pathologische Anatomie der Pilzvergiftungen., Inaug. Dissert., München, 1915.

¹³ Umber, Deutsch. med. Wchnschr., 1916, 42, Heft 1, No. 21, 627.

¹⁴ E. Lyon, Med. Klin. Berl., 1916, xii, 237-263.

¹⁵ Henius, Deutsch. med. Wchnschr., 1916, xlii, 701.

¹⁶ Fahr, Münch. med. Wchnschr., 1917, lxiv, 1436.

¹⁷ H. Schultze, Münch. med. Wchnschr., 1917, lxiv, 806.

Schmidt,¹ who gave a detailed description of the lesions with an extensive microscopic examination. In 1917 also Schuster² reported 13 cases of mushroom-poisoning. In 7 cases the Schierlingspilze (*Amanita phalloides*) was eaten by mistake for *Agaricus sylvicola*, Vitt (Waldechampignon). In 2 cases *Amanita phalloides* was mistaken for the woods mushroom and in 3 cases young forms of *Amanita phalloides* were mistaken for *Boletus edulis*, Bull (Steinpilz). In 1 instance *Amanita muscaria* was gathered and eaten because of its attractive appearance. Schuster differentiates between *Mycetismus intestinalis* produced by *Amanita phalloides* and *Mycetismus cerebialis* produced by *Amanita muscaria*. There were no deaths in his series.

In the year 1918 a number of important papers appeared. Zöllner³ reported a non-fatal case of poisoning from *Amanita verna*. Miller⁴ described in detail the pathologic anatomy in 4 fatal cases of phalloides intoxication, and Herzog⁵ reported 2 instances of poisoning from *Amanita phalloides*. In 1 instance 10 people were poisoned, of whom 6 died, and in the other 5 were poisoned, with 1 death. Herzog reported at length upon the lesions found at autopsy in 6 fatal cases. In 1918 also Kobert⁶ reported a large series of cases from Rostock, his final contribution to this subject.⁷ This series included 4 cases of poisoning from *Amanita phalloides*, with 3 deaths, in Rostock, 4 cases, with 4 deaths, in Lübeck, and 2 severe cases, with recovery, in Dessau. Kobert also reported 34 cases of poisoning from *Amanita regalis* (König-fliegenpilz) all of whom showed symptoms of muscarin intoxication, but recovered. Finally, he stated that 2 instances of lorchell poisoning had occurred recently in Rostock, 1 in 1917, all recovering, and 1 in 1918, with one individual dying. Stahl⁸ in 1918 reported 6 cases of morell (helvella?) poisoning, of whom 1 died, and von Jagie and Lipiner⁹ in the same year noted 19 cases of poisoning from *Amanita phalloides* or some kind of russula. The individuals showed gastro-intestinal symptoms and in 2 fatal cases the lesions pointed to *Amanita phalloides* intoxication. The following year Böttcher¹⁰ noted 2 cases from *Amanita phalloides*, and Prym¹¹ reported 8 deaths from poisonous mushrooms, the pathologic examination revealing the lesions due to this fungus. In 1920 Blank¹² described 11 cases of poisoning from fungi thought to be *Amanita phalloides*, with 2 deaths. Blank called special attention to the amuria in some of his cases and emphasized the importance of paying particular attention to the kidneys in the treatment. In this year also Fahrigr¹³ described 3 non-fatal cases of poisoning from a new species of inocybe, *Inocybe lat-varia*, von Ricken (Ziegel-roter R'sspilz) and gave references to 2 other cases, 1 fatal, reported by Dittrich¹⁴ from *Inocybe frumentacea*, 2 severe cases of poisoning from *Inocybe repanda*, also reported by Dittrich,¹⁵ and 1 case from *Inocybe sambucina* reported by Hermann.¹⁶ Finally, in 1920 Treupel and Rehorn¹⁷ reported 4 cases of *Amanita phalloides* intoxication, with 1 death, and Eugen Fränkel¹⁸ described minutely the lesions in 4 fatal cases of poisoning from the same fungus.

This gives an approximate total for Germany and Austria of about 171 cases, with 49 deaths, of which 105 were due to *Amanita phalloides*, with 44 deaths; 22, due to helvellas (morells?), with 4 deaths; 9 to inocybes, with 1 death, and 35 to *Amanita muscaria*, with no deaths.

In America a large number of cases of poisoning by mushrooms have occurred during the past fifteen years, and a number of important contributions to the sub-

¹ Schmidt, Zeitschr. f. ang. Anatomie, 1918, iii, 146-162.

² Schuster, Münch. med. Wehnschr., 1917, lxiv, 119.

³ Zöllner, Deutsch. med. Wehnschr., 1918, xlv, 213.

⁴ Miller, Berl. klin. Wehnschr., 1918, iv, 1164-1170.

⁵ Frank Herzog, Ztschr. f. Path., Wiesb., 1918, 21, 297-320.

⁶ Kobert, Deutsch. Arch. f. klin. Med., 1918, cxvii, 47-75.

⁷ Prof. Kobert has recently died.

⁸ Stahl, Med. Klin., Berlin, 1918, xiv, 1229-1232.

⁹ von Jagie and Lipiner, Wien. klin. Wehnschr., 1918, xxxi, 1029-1032.

¹⁰ Böttcher, Ztschr. f. d. ges. Neurol. u. Psychiat., Berlin, 1919-20, liii, 166-168.

¹¹ Prym, Virchow's Archiv., 1919, 226, 229.

¹² Blank, Münch. med. Wehnschr., 1920, lxvii, 1032-1034.

¹³ Fahrigr, Arch. f. exp. Path. u. Pharm., 1920, lxxviii, 227-246.

¹⁴ Dittrich, Ber. d. deutsch. bot. Gesellsch., 1916, Bd. 34.

¹⁵ Ibid., 1918, Bd. 36.

¹⁶ Hermann, Der Pilz-urd Kräterfreund, 1919, Bd. iii, Heft 1.

¹⁷ G. Treupel and E. Rehorn, Deutsch. med. Wehnschr., 1920, xlv, 509-540.

¹⁸ Eugen Fränkel, Münch. med. Wehnschr., 1920, lxvii, 1193.

ject have been made. In 1907 Jennings¹ described the poisoning of 5 persons, with 1 death, from eating a mixture of mushrooms including *Amanita phalloides*, *Amanitopsis vaginata*, *Russula emetica*, and some variety of *cantharellus* (cited from Fischer). In 1914 Bagnall² reported 9 cases of poisoning from unidentified fungi in the vicinity of Hartford, Connecticut. Bagnall states that there were 30 cases, with 12 deaths, in the season of 1905, 15 to 16 deaths in 1906, and 22 deaths in the vicinity of New York City in 1911 in one ten-day period during heavy September rains. There were also a large number of cases in the vicinity of Hartford in 1913, 26 in a few weeks. In one of Bagnall's cases, which later proved fatal, he noted the complete cessation of urine and recognized the importance of attention to the kidney complications. In the 8 other cases energetic measures were taken to relieve the kidney, and these cases recovered. In 1914 Verrill³ reported 2 cases of non-fatal intoxication from *Panaeolus papilionaceus*, and in the same year Vinnedge⁴ noted 3 fatal cases from unidentified fungi. In 1915 Clark, Marshall, and Rowntree⁵ made a very important contribution to the subject, carefully studying the kidney function in a chronic and fatal case of poisoning due in all probability to *Amanita phalloides*. They state further that in the season of August and September, 1914, 30 cases of mushroom poisoning occurred in Baltimore, with 7 deaths. Finally, in 1920 Alexander⁶ called attention to the renal glycosuria and nephritis in 5 individuals poisoned with fungi thought to be *Amanita muscaria*, and in 1921 Roberts⁷ reported a non-fatal case of poisoning by *Clitocybe sudorifica*. In addition to these reports of cases observed in this country, in 1918 Fischer⁸ published an elaborate thesis on the subject in which he has added a number of interesting and valuable observations to our knowledge.

In addition to the cases of mushroom intoxication which have been reported in the medical journals there are many cases described in the newspapers which do not get into the medical literature. Thus the present writer has newspaper records of 15 deaths in over 32 cases none of which have been reported medically, and Fischer states that he has records of 77 cases, with 16 deaths, in a ten-year period for southeastern Michigan alone.

In Japan cases of mushroom-poisoning have been described by Ichimura⁹ from a new species of *clitocybe*, *Clitocybe acromelalga*.

AMANITA PHALLOIDES

The most frequent cause of mushroom-poisoning is *Amanita phalloides*, Bulliard, the white, or deadly amanita. This species has been described under a great many different names, such as *Amanita bulbosa*, Persoon, and its varieties—*alba*, *citrina*, *virescens*, and *olivacea*; *Agaricus bulbosus*, Bulliard; *Amanita viridis*, Persoon; *Amanita mappa*; *Amanita virosa*, Fries; *Amanita venenosa*, Persoon. The terms *Amanita recucita*, Fries, and *Amanita porphyria*, Fries, probably indicate the same species. In French literature it is known as "l'orange ciguë," "l'orange blanche ou citronnée," "l'orange ciguë jaunâtre," and "l'orange souris." In Germany it is usually called the "Knollenblätterschwamm." In England and in America the term "toadstool" is usually popularly employed for the species, but not exclusively. In Austria it is called the "Schierlingspilz." The spring form is usually called the *Amanita verna*, but grows also in summer and autumn.

¹ O. E. Jennings, Jour. of Mycol., September, 1907, and Mycol. Bull., February, 1908, vi, No. 86. Cited from Fischer.

² Bagnall, Boston Med. and Surg. Jour., 1914, clxxi, 111-113.

³ A. E. Verrill, Science, 1914, n. s., xi, 408-410.

⁴ Vinnedge, Indian. Med. Jour., 1914, xvii, 432-434.

⁵ Clark, Marshall, and Rowntree, Jour. Amer. Med. Assoc., 1915, ix, No. 4, April 10, 1230-1232.

⁶ Alexander, Amer. Jour. Med. Sci., 1920, clxx, 543-548.

⁷ J. W. Roberts, Mycologia, 1921, xiii, 42-44.

⁸ Fischer, Agaricaceæ of Michigan, Publication 26, Biological Series 5. Michigan Geological and Biological Survey, December, 1918.

⁹ Ichimura, Bot. Gaz., 1918, 65, 109-111.

The predominance of poisoning from this species over that from other species is indicated by the statistics of Gillot,¹ who reported 115 cases, with 73 deaths, a mortality of 63 per cent. In the cases previously reported by the author,² 204, with 153 deaths, were traced to species clearly identified as *Amanita phalloides*, a mortality of 75 per cent.; while 32 cases, with 22 deaths, showed the clinical symptoms of "phalloides" intoxication. Roch³ reported 381 cases, with 188 deaths, a mortality of 49 per cent. This lower figure for mortality is probably more nearly correct, since in most collections of cases autopsy reports are included, and often mention is made of non-fatal cases occurring at the same time, but the number is not given. This is borne out by more recent statistics from the French and Swiss literature which

showed 556 cases, with 262 deaths, from *Amanita phalloides*, a mortality of 47 per cent., and 105 cases, with 44 deaths, from the German and Austrian literature, a mortality of 41.9 per cent.



FIG. 74.—*Amanita phalloides* (death-cup).

There are several reasons for this predominance of poisoning from *Amanita phalloides*. It is in the first place very abundant, especially at certain seasons of the year, and has an excellent taste, so that no warning is given its victims at the time of ingestion. Then a very small quantity, a portion of one plant even, can produce fatal intoxication, especially if the fungus is eaten raw. Thus Plowright⁴ has reported the death of a boy of ten years from eating one-third of the pileus of a small plant identified as *Amanita verna* (the spring form of *Amanita phalloides*), and a number of instances have

occurred where one or two specimens were sufficient to bring on fatal results. Probably the most important reason of the high mortality lies in the lesions produced in the internal organs, since these are of such a character as to resist any medicinal treatment.

Botanical Characters.—The usual specimens of *Amanita phalloides*, the "white or deadly amanita," grow to a height of 4 to 6 inches, the stalk being $\frac{1}{2}$ to $\frac{3}{4}$ inch in diameter, and the upper expanded top or pileus having a diameter of 3 to 4 inches. The stalk is set in an expanded cup or volva often called the "poison cup," which is set in the ground sometimes at a considerable depth and attached by fine threads of mycelium to the roots below. On the lower part of the stalk there may be small, rather feathery, flakes which are easily brushed off and which are remnants of the universal volva in which the growing plant was originally enclosed. The upper part of the stalk has attached to it a filmy, delicate ring or annulus about $\frac{1}{2}$ to 1 inch from the junction of the pileus and the stalk. This is often adherent to the lower part of the pileus. The pileus is usually smooth on top and is provided on its under surface with a series of gills sometimes still covered by the annulus or veil. Attached

¹ Gillot, *Étude medicale sur l'empoisonnement par les champignons*, Lyon, 1900.

² Ford, *Johns Hopkins Hosp. Bull.*, April, 1907, xviii, No. 193, 123.

³ M. Roch, *Les empoisonnements par les champignons*, Geneva, 1913.

⁴ Plowright, *Lancet*, 1879, 2, December, 941.

to the gills are the spores, pure white in color. The entire plant is of a peculiar dead white, except the upper portion of the pileus, which may be chalky white, smoke colored, delicately yellow or slightly greenish. Many botanists separate the species into different varieties according to the color of the pileus. As the plants mature they take on a somewhat obscure dirty brownish-white color, and as they begin to decay they are often grayish brown. The form which often appears in the early spring is smaller and pure white in color. This is usually called *Amanita verna* or the "destroying angel" of Bulliard. It is indistinguishable from *Amanita bisporigera* of Atkinson. The "deadly amanita" is very common in woods and along the borders of roads, especially during the latter part of August and September. It usually grows singly. When dried it has quite a characteristic odor (fatty acid?).

Symptoms of *Amanita Phalloides* Intoxication.—The symptoms of poisoning from *Amanita phalloides* are characteristic and unmistakable. They begin to come on after a distinct prodromal stage of six to fifteen hours, being ushered in by extreme abdominal pain, vomiting, and diarrhea. Both vomitus and stools contain undigested food, blood, and mucus. There is rarely constipation. The urine is usually straw-colored, not tinged with hemoglobin. Anuria is seen not infrequently and is especially important. Paroxysms of pain and vomiting alternate with periods of remission which however are usually brief. The extreme suffering usually brings on the "Hippocratic facies," "la face vultueuse" of the French writers. The loss of strength is rapid and excessive. Jaundice, cyanosis, and coldness of the skin, especially of the extremities, develop within two or three days. The course of the disease is from four to six days in children and six to eight days in adults. Before death the patients often sink into a profound coma from which they cannot be roused. Ocular symptoms such as trismus are rare and the pupils are usually normal in size, reacting to light and accommodation. Nervous and mental symptoms occasionally occur, but convulsions are rare except as a terminal event, and in children. When large quantities of the fungus are eaten a very profound intoxication may develop, death occurring within forty-eight hours. The mortality varies greatly according to the amount of the plants eaten and according to the age of the individuals. There are many instances where every person who partook of the meal has succumbed, a mortality of 100 per cent., while in other cases only 1 or 2 have survived. In statistics based upon large numbers of cases the mortality may vary from 50 to 70 per cent. Young children are highly susceptible and in general are less apt to survive than adults. The majority of cases are produced by well-cooked plants, but those who eat the fungi raw are apt to be more profoundly poisoned. One or two specimens, a single specimen, or even a part of a specimen may bring on a violent poisoning and death. Rarely chronic intoxication develops, the patients surviving three to four weeks. In the non-fatal cases the serious symptoms begin to subside in six to eight days and the patients slowly recover, being restored to normal health and strength in about a month. In addition, many cases of less profound intoxication are seen due to the ingestion of small quantities of the plants and here the violent gastrointestinal symptoms may subside rapidly, the patients recovering in a few days.

In recent cases of poisoning by *Amanita phalloides* especial attention has been called to the symptoms arising from the kidneys and the nervous system. Thus Bagnall¹ noted the nephritis and anuria in a fatal case probably due to *Amanita phalloides* and acting upon this hint paid special attention to treatment of the kidneys in 8 other cases of mushroom-poisoning, all of whom recovered. Clark, Marshall, and Rountree² studied with great care an individual who died twenty-eight days after eating mushrooms, undoubtedly *Amanita phalloides*. They noted especially bleeding from the gums and rectum, symptoms not previously observed, and an impaired kidney function. Tested by the phenolsulphonephthalein method the renal function was but 3 per cent. in a two-hour period. At autopsy there was an epithelial necrosis of the kidney in addition to a central necrosis of the liver, and an acute enteritis and colitis. These authors suggest that the nervous and mental symptoms often seen in this type of intoxication may be uremic in character. Schultze³ also emphasized the nervous and ocular symptoms, such as trismus, in 6 cases observed by him. Schürer⁴ previously in a report of 6 cases had noted cramps and convulsions in a child of five years who ate large portions of *Amanita phalloides*. At autopsy degenerative changes were found in the cells of the central nervous system. Still earlier Rem-Picci⁵ had described 6 cases of poisoning by fungi which were probably *Amanita phalloides*. Of these 6 cases 3 showed nephritis and 1 case epileptic cramps with rolling of the eyes and foaming at the mouth. Three of the patients died and at autopsy the lesions were characteristic of "phalloides" intoxication. Metabolism experiments were carried out in 2 cases, showing increased protein decomposition with a lessening of the urea nitrogen and an increase of the ammonia nitrogen. Rem-Picci concluded that considerable amounts of acid were stored in the tissues as in phosphorus-poisoning. According to Thiemich⁶ glycosuria occurs in *Amanita phalloides* poisoning.

ILLUSTRATIVE CASES

Typical cases of poisoning by *Amanita phalloides* were reported by Pfrom⁷ in 1905. A family of Italians living in Minalola, New Jersey, consisting of father, mother, and 4 children partook of a stew of mushrooms on the evening of July 15, 1905. The parents ate large quantities of the fungi, the children dipping pieces of bread in the stew and eating these. About midnight symptoms of poisoning came on consisting of vomiting, pain in abdomen, thirst, headache, and constipation. In the morning at 7 A. M. the father was cyanotic, prostrated, and showed vomiting and muscular twitching in the chest. By 8 A. M. he was delirious, pupils contracted, eyes glazed. During the day he was more comfortable, but the symptoms returned in the evening. He exhibited paroxysms of pain from then on about every twelve hours. He was taken to the Medico-Chirurgical Hospital in Philadelphia, where he showed retching and vomiting, pain in the chest with difficult breathing, thirst, attacks of hiccup every two hours, contraction of the muscles of the face, "la face

¹ Bagnall, Boston Med. and Surg. Jour., 1914, clxxi, 111-113.

² Clark, Marshall, and Rountree, Jour. Amer. Med. Assoc., 1915, ix, No. 4, April 10, 1230-1332.

³ H. Schultze, Münch. med. Wehnschr., 1917, lxiv, 806.

⁴ J. Schürer, Deutsch. med. Wehnschr., 1912, xxxviii, 548-551.

⁵ G. Rem-Picci, Cited in Schmidt's Jahrbucher, 1903, 278, 134.

⁶ Thiemich, Deutsch. med. Wehnschr., 1898, 24, No. 48, 760.

⁷ G. W. Pfrom, Med. Bull., Phila., 1905, xxvii, November, 401-404.

vulteuze," and an uncontrollable diarrhea, the stools being small, greenish, and bloody. He developed cyanosis and died of dyspnea on the eighth day after eating the fungi. The mother showed similar thirst, prostration, vomiting, rapid pulse, and aborted a five-month fetus. She rapidly developed cyanosis, delirium, coma, and died of heart failure on the eighth day. She had a slight fever, temperature 99° to 101° F., and her urine was bloody. The children, aged two and seven years, suffered from the same pain and vomiting, but rapidly developed unconsciousness, dying in fifty-eight to fifty-nine hours after swallowing merely the juice of the mushrooms.

Another, typical instance was reported in the same year by Plowright,¹ who described 6 cases and 4 deaths occurring in the country districts of England. In one instance a boy of twelve years ate about one-third of the pileus of a raw *Amanita phalloides* at 11.30 in the morning. At 1 o'clock the next morning, thirteen hours after eating the mushroom, he began to suffer from vomiting, diarrhea, and great thirst. The next day he was better, eating breakfast at 8 A. M., the vomiting and diarrhea returning at noon. The next day he was again better, but later developed the same symptoms with severe abdominal pain. On the fifth day he had slight convulsions and died eighty-one hours after ingesting the fungus.

In another case a boy of five years ate an unknown quantity of *Amanita phalloides* about 4 o'clock in the afternoon. The same night, ten to twelve hours after eating the fungi, he began to have diarrhea, severe abdominal pain, and intense thirst. On the evening of the second day he sank into a coma, and died on the third day, sixty-eight hours after the mushrooms were consumed.

In the third instance a man of thirty-two gathered *Amanita phalloides* and with his wife, aged twenty-two years, daughter, aged seven, and son, aged one year and seven months, ate altogether between 3 and 4 pounds. The mother and boy ate the fungi raw. The next day the mother and son were taken sick at 6 A. M.; somewhat later the father and daughter. The symptoms were diarrhea, vomiting, thirst, perspiration, and intense crampy pain in the abdomen, located in the epigastrium. The boy developed convulsions, distortion of the muscles of the face, nystagmus, and dilated pupils, dying fifty-four hours after eating the mushrooms. At autopsy there was jaundice, swelling of the mucous membrane of stomach and intestine, enlarged mesenteric glands, an enlarged pale yellow liver, and a congestion of the kidneys and spleen.

The mother developed jaundice on the third day and suffered great pain, which was paroxysmal and cramp-like in character. She aborted a three-month fetus. On the fourth day she was very restless, with retracted head, almost unconscious, with complete anuria. She developed irregular respiration, Cheyne-Stokes in character, and died about one hundred hours after eating the fungi.

The father developed the same pain, diarrhea, and vomiting with perspiration. He had the pinched and protracted facies of "la face vulteuze." On the eighth day he became better and slowly recovered. The daughter developed diarrhea with stools stained with blood and mucus, great thirst, and an enlargement of the liver. No fever. Her diarrhea gradually subsided and she slowly recovered.

These cases are remarkable in that two of the individuals were severely poisoned but recovered.

Pathologic Lesions.—The changes found at autopsy in fatal cases of *Amanita phalloides* intoxication are quite characteristic. They were described first by Maschka² over half a century ago. According to Maschka they consisted essentially of lack of postmortem rigidity, widening of the pupils, failure of the blood to coagulate, and a cherry-red color, ecchymosis and hemorrhage in the serous membranes and the parenchymatous organs; dilatation of the bladder with urine. Maschka also noticed a fatty degeneration of the internal organs, but failed to regard this lesion with the attention it deserved. Subsequently Carayon³ in 1873 investigated the lesions in the bodies of soldiers who had died three days after eating cooked *Amanita phalloides*. He noted

¹ Plowright, Brit. Med. Jour., 1905, ii, 541.

² Maschka, Vrtljschr. f. d. prakt. Heilk., 1855, 46, 137.

³ Carayon, Gaz. d. hôp., 1873, 1115.

an inflammation of the walls of the stomach and intestines, a congestion of the liver and kidney, a dark red and fluid condition of the blood, and in one case a congestion of the meninges. He thus confirmed Maschka's observations in part, but failed to note the fatty degeneration of the internal organs. A little later Chouet and Pelissié¹ studied the lesions in two individuals who died in forty-eight and in sixty hours after ingesting the fungi. They noted particularly the hemorrhages into the stomach and intestines, with ecchymosis in the gastric mucosa and in the liver. The most important observations possibly were those of Sahli² in 2 cases. He found the gross lesions described by Maschka, including the subpleural and intrapulmonary hemorrhages, and noted in addition a general atrophy of the panniculus adiposus. Microscopically, he found a fatty degeneration of the heart muscle, the kidney, the liver, and the diaphragm as well as in the voluntary muscles such as the pectorals, deltoid, abdominal, and the tongue. The amount of the fat in the liver was so great as to remind him of acute phosphorus-poisoning with which *Amanita phalloides* intoxication has ever since been compared. He also found a congestion of the stomach and intestines and swollen Peyer's patches and solitary follicles. Similar lesions were found by Handford³ and by Tappeiner.⁴ Tappeiner noted also the fatty degeneration of the liver and kidney with cellular infiltration and infarcts, like the lesions seen in phosphorus-poisoning, with similar infarcts in the heart muscle, which also was fatty. The percentage of the fat in the liver was estimated by Tappeiner in these 2 cases. He found 53.6 per cent. in one case and 68.9 per cent. in the other. According to Perls the fat content of the liver in normal individuals varies from 8 to 12 per cent. The percentage of fat in the liver in cases of *Amanita phalloides* intoxication thus closely approximates that found in phosphorus-poisoning which varies from 50 to 70. The percentage of liver fat found by Tappeiner was confirmed by Thiemich,⁵ who estimated it in one case at 69.1 to 69.3 per cent., and in another at 73.1 to 73.5 per cent.

Three cases were subsequently described by Moers,⁶ who noted especially the hemorrhages into the stomach and intestines, on the surface and in the substance of the liver and kidney, in the heart and pericardium, the external coat of the aorta, in the ovary, and in the brain. It is interesting to note that in these 3 cases the organs were tested for arsenic, phosphorus, and muscarin, and in the absence of these substances the lesions could only be attributed to the fungi which had been ingested. Subsequently Plowright⁷ found in addition to the usual lesions gangrenous spots on the mucous membrane of the intestines

¹ Chouet and Pelissié, *Gaz. hebd. de Méd.*, 1880, 2d s., 17, 68.

² Sahli, See Studer, Sahli and Schärer, *Nitth. der Naturfors. Gesellsch.*, 1885, p. 81.

³ Handford, *Lancet*, 1886, 2, 1018.

⁴ Tappeiner, *Münc. med. Wchnschr.*, 1895, 42, 133.

⁵ Thiemich, *Deutsch. med. Wchnschr.*, 1898, 24, No. 48, 760.

⁶ Moers, *Ztschr. f. med. Beamt.*, 1903, 16, 412.

⁷ Plowright, *Brit. Med. Jour.*, 1905, ii, 541.

and a general peritonitis in one case with much enlarged solitary follicles in the intestines.

While these observations give us a clear picture of the lesions in *Amanita phalloides* intoxication, they were reported some years ago and the material was not studied by modern methods. Recently, however, a number of important studies of the pathology of this condition have appeared in the German literature and our knowledge of the lesions has been made much more exact. Schürer¹ in an autopsy on a child of five years which died thirty-five hours after eating fungi thought to be *Amanita phalloides*, noted an inflammation of the ileum and colon; swelling of the mesenteric glands; fatty degeneration of the heart and skeletal muscles; fatty degeneration of the liver, particularly in the periphery of the acini; fatty degeneration of the kidney and advanced degenerative changes in the cells of the central nervous system. His microscopic examination revealed no evidences of hemolytic changes. Schürer regarded the fatty degeneration of liver, kidney, heart, and skeletal muscles in combination with swelling of the follicles and Peyer's patches in the intestines, as pathognomonic of *Amanita phalloides* poisoning.

Several years later Fahr² reported an autopsy upon a case of "phalloides" intoxication, finding the usual lesions. On microscopic examination of the organs he noted the presence of doubly refractile fat (cholesterin esters) in the kidneys. The usual changes were also noted by Kobert³ and by Schmidt⁴ in his autopsies on Schultze's cases. In 1918 Herzog⁵ described with great care the lesions in 6 individuals who died three to four days after a meal of *Amanita phalloides*. He observed advanced destruction of the cells of the liver with much fatty infiltration, together with hemorrhages and a leukocytic infiltration. He also noted a beginning regeneration of the liver—a reproduction of bile-ducts with many mitotic figures and fat drops in the cells. These cells were apparently taking the place (Ersatz) of the destroyed liver cells. Herzog observed also a great destruction of liver cells which showed no fatty degeneration, a condition similar to that described by Paltauf⁶ in acute atrophy of the liver. The kidneys, heart muscle, and the pancreas likewise showed fatty degeneration and large hemorrhages were present in the splenic pulp. In 3 cases there were erosions of the mucous membrane of the stomach. Herzog regarded the lesions in *Amanita phalloides* intoxication as characteristic and the disease hepatogenous in origin. In the same year Miller⁷ described the pathologic anatomy of 4 cases which he believed to be "phalloides" poisoning. He called special attention to the minute and massive hemorrhages in the intestines and to the absence of jaun-

¹ J. Schürer, Deutsch. med. Wchnschr., 1912, xxxviii, 548-551.

² Fahr, Münch. med. Wchnschr., 1917, lxiv, 1436.

³ Kobert, Deutsch. Arch. f. klin. Med., 1918, cxxvi, pp. 47-75.

⁴ Schmidt, Zeitschr. f. ang. Anatomie, 1918, iii, 146-162.

⁵ Frank Herzog, Ztschr. f. Path., Wiesb., 1918, 21, 297-320.

⁶ Paltauf, D. path. Gesellsch., 1902, p. 91.

⁷ Miller, Berl. klin. Wchnschr., 1918, iv, 1164-1170.

dice. On microscopic examination he found frequent degeneration and fatty infiltration of the endothelial cells of the blood-vessels, degeneration and fatty infiltration of the epithelial cells of the adrenals, with an increase of lipoid material and advanced fatty degeneration of the cells of the kidney, many of which were totally replaced by fat. The liver showed an excessive fatty degeneration resembling in its gross appearance the famous "goose-livers" of Strassburg. The liver in 2 cases showed an extensive deposition of a pigment giving the reactions of hemosiderin, and in 2 cases an iron-negative lipochrome pigment. There was in addition a general leukocytic infiltration in the liver especially about the bile-ducts. The heart showed fragmentation and fatty deposition in the papillary muscles and necrosis and fatty deposition in the muscles of the myocardium. The skeletal muscles also were the seat of fatty degeneration. In the nervous system Miller found degenerative lesions of the cells, with a deposition of fat, changes similar to those previously described by Schürer. Miller concluded that the anatomic picture was characteristic of *Amanita phalloides* intoxication. The next year Prym¹ made a careful study of the organs in 7 individuals who had died from eating mushrooms which were probably *Amanita phalloides*. He also observed the typical hemorrhages in the serous membranes and organs, the fatty degeneration of the heart muscle, liver, and kidney. In the liver he noted an attempt at regeneration in the older cases in the connective tissue and in the bile-ducts. In another case sent to him for diagnosis he also found many new bile-ducts. The kidneys showed a beginning inflammation of the glomeruli. Prym confirmed the previous observations of Fahr in that he also found doubly refractile substances in the fat in the liver and kidney. He agrees with previous writers as to his pathologic findings, but sees no essential difference between *Amanita phalloides* poisoning and acute yellow atrophy of the liver, or phosphorus-poisoning. He suggests however that the presence of doubly refractile fat in the liver and kidney may prove to be a point of differential diagnosis between fungus intoxication and phosphorus-poisoning since, in the latter only simply refracting substances are present in the fat. He would regard the pathologic finding as characteristic, but not pathognomonic. Finally, excellent descriptions of the pathologic changes have been given recently by Treupel and Rehorn,² who have added an important discussion of liver function in this connection, and by Fränkel,³ who described minutely the pathologic changes in 4 autopsies.

From these exhaustive examinations it is evident that we have in *Amanita phalloides* intoxication the action of a poison which produces wide-spread destruction of cells, including the endothelial cells of the blood-vessels, cells of the voluntary and involuntary muscles, epithelial cells of the kidney, the epithelial cells of the adrenal, the liver cells, and the cells of the central nervous system. This destruction seems to be so

¹ Prym, Virchow's Archiv., 1919, 226, 229.

² Treupel and Rehorn, Deutsch. med. Wchnschr., 1920, xlv, 509, 540.

³ E. Fränkel, Münch. med. Wchnschr., 1920, lxvii, 1193.

wide-spread as to preclude the recovery of the patient. The attempts at regeneration on the part of the liver observed by several authors indicate however that the injury inflicted is not beyond repair. Whether all the lesions seen at autopsy in man are due to a single poison or whether more than one poisonous substance is present in the fungus can be determined only by careful study of the fungus itself and its effect upon animals.

Lesions in Animals.—Subcutaneous administration of small quantities of aqueous extracts of *Amanita phalloides* is fatal to small animals such as rabbits and guinea-pigs (Ford¹). The animals usually die after the lapse of four to six days, but may succumb to large doses within twenty-four to forty-eight hours. At autopsy an extensive gelatinous edema is found in the subcutaneous tissues at the site of inoculation, the edematous tissue exuding a thin, reddish fluid on pressure. Minute hemorrhagic areas are visible everywhere in the neighboring fascia and muscular tissues, while the adjacent lymphatic glands are swollen and hemorrhagic. In the abdominal cavity the blood-vessels are much injected, and there are widespread hemorrhages varying in size from small ecchymoses on the surface of the liver and kidney to considerable collections of blood in the layers of the peritoneum. Congestion and hemorrhage are also marked in the pleura, lungs, liver, kidney and adrenals, and in the lymphatic glands of the abdominal cavity. In female animals hemorrhages are present in ovaries and uterus. The urine in the bladder is deeply stained with blood pigment showing no intact blood-corpuscles on centrifugation, a true hemoglobinuria. The heart is usually in diastole. The contents of the stomach and intestine are blood-stained, minute ulcers in the mucosa of the bowel with extravasated blood at the base of the ulcers indicating the source of these hemorrhages.

On microscopic examination the connective and muscular tissue is much swollen, the muscle-fibers show hyaline degeneration, and extravasated blood-corpuscles are found near the blood-vessels and between the muscle bands. The lymphatic glands are everywhere congested and hemorrhagic, the lymph-cells are necrotic with pyknotic nuclei, and there is a general increase of pigment. In the spleen there is always considerable extravasated blood, but the most noticeable change is the very great increase of blood-pigment, while the cells of the splenic pulp are necrotic with pyknotic nuclei. The vessels of the liver are generally congested and many blood-corpuscles lie free in the inter- and intralobular spaces and between the hepatic cells. Rarely one can find a break in the lumen of some one of the smaller capillaries and a direct connection between this break and the areas of extravasated blood. The nuclei of the capillary endothelium are pyknotic, the liver cells are necrotic, and there is a general increase of pigmentation. In the kidney there is a similar condition of congestion and hemorrhage. The kidney cells are shrunken from the basement membrane and are the seat of hyaline degeneration. The lungs show extensive vascular dilatation with many free blood-corpuscles in and between the alveoli and an excess of blood-pigments. The muscle-fibers of the heart exhibit hyaline degeneration, nuclear vacuolation, and at times almost complete destruction extending to the formation of small areas of focal necrosis. Finally, all the organs show extensive fatty degeneration, the fat being widely distributed, especially in the liver and kidney.

From this resumé it is evident that the lesions found in animals injected subcutaneously with the fungus differ markedly from those described in man. The most marked lesion is possibly the extensive blood destruction as evidenced by the hemoglobinuria and the marked pigmentation. In addition we have a widespread congestion and numerous hemorrhages similar to those described in the human cases of poisoning and an extensive destruction of the cells of all the organs and of the lymphatics with abundant deposition of fat. We thus have the characteristic lesions observed in man and in addition to these, changes which can be attributed to extensive blood destruction. It should be emphasized that these lesions in animals follow subcutaneous administration of extracts of the raw fungus. Neither rabbits nor guinea-pigs seem to be susceptible to the action of the fungus administered by the alimentary canal. The digestive juices in man exercise a profound influence upon the poison in *Amanita phalloides* and the lesions in man are attributable to certain of its constituents which withstand heating and the action of the gastric ferments.

Active Principle of Amanita Phalloides.—The first attempt to obtain the active principle of *Amanita phalloides* by experimental

¹ Ford, Jour. Inf. Dis., 1908, 5, No. 2, 116-132.

work on animals was that of Letellier¹ in 1826, who obtained a highly resistant body from a considerable variety of fungi including *Amanita phalloides*, *Amanita verna*, and *Amanita muscaria*. This substance he called amanitin. Subsequently Letellier and Spenceux² obtained two poisons from a fungus found in the vicinity of Paris known as *Hypophyllum cruz melitense*, probably a variety of *Amanita phalloides*. One of these poisons caused a violent inflammation of the mucous membrane of the alimentary canal in cats, with vomiting and diarrhea. The other substance was described as purely narcotic in its action. It was regarded as identical with the amanitin previously described by Letellier and because of its ability to reduce copper solutions was regarded as a glucosidal alkaloid. Subsequently, Boudier³ in 1866 named the active principle of *Amanita phalloides* bulbosin, and Ore⁴ in 1877 named it phalloidin. Neither investigator succeeded in isolating the principle by chemical methods.

From this time little of importance was added to the toxicology of this fungus till Kobert,⁵ in 1891, made the important observation that aqueous and saline extracts of dried *Amanita phalloides* are powerfully hemolytic or hemotoxic, dissolving the corpuscles of a variety of animals in dilutions as high as 1 : 125,000 of the dried material. This substance was named *phallin* by Kobert and was first regarded by him as the active principle despite the fact that it was highly unstable, easily rendered inactive by exposure to a temperature of 70° C. (158° F.) and by contact with weak acids, alcohol, and other agents. Because of the fact that extracts of this blood-laking material contained a little coagulable protein and resembled a hemolytic poison secreted by certain spiders Kobert concluded that the blood-laking poison of *Amanita phalloides* is a toxalbumin. Subsequently Seibert,⁶ working in Kunkel's laboratory, was unable to find any hemolytic substance in *Amanita phalloides*, although extracts of the fungus were definitely toxic to small animals, and on the basis of this work Kunkel concluded that phallin cannot be the active principle. Finally Kobert,⁷ in 1899, found a highly poisonous substance in alcoholic solutions of *Amanita phalloides*, and because these solutions gave precipitates with certain alkaloidal reagents he concluded that the active principle of the fungus is an alkaloid.

In 1906 and 1908 Ford⁸ showed that saline and aqueous extracts of all true specimens of *Amanita phalloides* are powerfully solvent to the corpuscles of a great variety of animals and that these solutions lose their blood-laking activity after heating to 70° C. (158° F.), exposure to weak acids and alkalis, and to the digestive juices, pepsin and pancreatin.

¹ Letellier, Thèse de Paris, 1826.

² Letellier and Spenceux, Annal. de hyg. pub. et de méd. leg., 1867, p. 71.

³ Boudier, Des champignons au point de vue de leurs caractères usuels, cliniques et toxicologiques, 1866.

⁴ Ore, Arch. de physiol. norm. et path., 1877, xi, 274.

⁵ Kobert, St. Petersburg, med. Wehnschr., 1891, xvi, 463, 471.

⁶ Seibert, Inaug. Dissert., Münch., 1893.

⁷ Kobert, Handb. d. Toxikol., 1901, II, 1048.

⁸ Ford, Jour. Inf. Dis., 1906, iii, 192-224; Jour. Exp. Med., 1906, viii, 437-450, Jour. Inf. Dis., 1908, 5, 116-132.

After such treatment the extracts remained highly poisonous to both rabbits and guinea-pigs on subcutaneous inoculation. The lesions consisted of wide-spread hemorrhages in the mucous membranes, in the serous membranes, and in the internal organs, with extensive degeneration of the cells of the liver, kidney, and voluntary and involuntary muscles, with the deposition of large quantities of fat in the cells. The changes were practically identical with the lesions in man. On the basis of these experiments it was concluded that the blood-destroying substance in *Amanita phalloides* cannot be the active principle and plays at most only a subsidiary rôle when the fungi are eaten raw. The active principle is the substance in the extracts of the plant which remains poisonous after cooking and after treatment with acid, alkalis, and the digestive ferments. For purposes of clarity the blood-laking substance in *Amanita phalloides* (thé phallin of Kobert) was named *Amanita hemolysin*, the non-hemolytic substance present in the extracts after heating, the *Amanita toxin*, the latter being regarded as the poison responsible for death in man after ingestion of the fungi. Subsequent chemical investigation of *Amanita phalloides* by Abel and Ford¹ demonstrated that on the treatment of aqueous extracts of the fungus with methyl alcohol a voluminous precipitate appears which contains the *Amanita hemolysin*, while the *Amanita toxin* remains in solution. The methyl alcohol precipitate taken up in water contains a very small amount of coagulable protein which may be removed by the addition of freshly prepared metaphosphoric acid and by uranyl acetate. After removal the solutions contain inorganic salts and a pigmentary substance, the great bulk of the solution being a glucosid which reduces Fehling's solution and ammoniacal silver nitrate, after hydrolysis with mineral acids gives an abundant precipitate with neutral or basic lead acetate and tannic acid and does not ferment with brewer's yeast. These solutions furthermore give several tests for pentoses including a purplish-violet color on heating gently with α -naphthol and sulphuric acid, a cherry-red color after similar treatment with phloroglucinol and hydrochloric acid, a deep green color on heating gently with orcinol, hydrochloric acid, and a drop of ferric chlorid solution. In addition, the solutions always contain nitrogen as evidenced by positive Laissaigne tests. On the basis of these and other reactions Abel and Ford concluded that the *Amanita hemolysin* is not a toxalbumin, but a nitrogenous glucosid easily decomposed by acids and yielding a pentose and a volatile base or bases such as ammonia and methylamin. Subsequently Abel and Ford² developed a method for isolating this glucosid and made a preliminary analysis which indicated the following elementary composition:

C.....	48.93
H.....	6.08
N.....	10.83
S.....	1.94

¹ Abel and Ford, Jour. Biol. Chem., 1907, ii, 273.

² Abel and Ford, Schmiedeberg Festschrift, 1908, Supplement-Band, Arch. f. exp. Path. u. Pharm.

The reactions of the isolated glucosid were practically the same as those of the original solution after freeing from protein and various impurities. The hemolytic strength of the solution remained intact and in certain preparations showed an activity in a dilution of 1 : 300,000, thus making it the most powerful blood-laking substance known. It was not, however, regarded by them as the active principle. This is contained in alcoholic solutions of the fungus and may be precipitated from these solutions by phosphotungstic acid. It has been shown by Schlesinger and Ford¹ that after several reprecipitations by phosphotungstic acid and the removal of impurities by such reagents as silver nitrate and basic lead acetate the *Amanita toxin* can be isolated in considerable purity. It was found to be highly resistant to boiling in aqueous and alcoholic solutions, to be slowly affected by acids at room temperature and rapidly destroyed by boiling acids. It did not reduce Fehling's solution either before or after prolonged treatment with 5 to 10 per cent. hydrochloric acid. The *Amanita toxin* did not react with any of the alkaloidal precipitants nor did it give any of the alkaloidal color reactions. It did not give the Biuret test or Millon's reaction. Because of these reactions the *Amanita toxin* was regarded by Schlesinger and Ford as neither a glucosid, an alkaloid, nor a protein in the generally accepted sense. Since, however, it contained nitrogen and sulphur, the latter as conjugate sulphuric acid, and on fusion with potassium hydrate gave off the odor of amines and indol and gave the characteristic pyrrol-red test, it was concluded by Schlesinger and Ford that the toxin is probably either an indol derivative or an aromatic phenol so combined with an amine group that it readily forms an indol or pyrrol ring. An analysis of a highly active preparation subsequently obtained by Ford and Bronson² gave the following elementary composition:

C.....	42.89
H.....	8.79
N.....	14.16
S.....	2.91

On injection into animals the *Amanita toxin* produces an acute intoxication in which the lesions closely resemble those seen in man in fatal cases, including the hemorrhages and the wide-spread necrosis and fatty degeneration of the cells of the internal organs, especially the liver and the kidney. With the evidence at hand there can be little question but that this body is the active principle. The *Amanita hemolysin* is also poisonous to small animals on subcutaneous inoculation, producing wide-spread destruction of the red blood-corpuscles with hemoglobinuria and microscopically an increased pigmentation, especially in the spleen and liver. Since these lesions are not observed in man the *Amanita hemolysin* probably has no effect when the cooked fungi are ingested. The lesions produced in animals by injection of the whole raw extract

¹ Schlesinger and Ford, Jour. Biol. Chem., 1907, iii, 279.

² Ford and Bronson, Jour. Pharm. and Exp. Ther., 1913, iv, 241.

appear to be a combination of the lesions produced by the poisons injected separately.

During the progress of these investigations Rabe,¹ working in Kobert's laboratory, stated that alcoholic solutions of *Amanita phalloides* produce a stoppage of the frog's heart in diastole in a Williams' perfusion apparatus, this effect being neutralized by atropin just as extracts of *Amanita muscaria* are neutralized by atropin solutions. On the basis of this work Rabe and Kobert concluded that *Amanita phalloides* contains a poison like muscarin. It has since been shown by Ford and Brush² that this stoppage of the frog's heart in diastole is due to the salts in the fungus extract and can be relieved by washing out the heart with Ringer and Locke's solution as well as by a solution of atropin. There is no evidence therefore that *Amanita phalloides* contains an alkaloidal substance like muscarin. Subsequently Kobert³ suggested the presence of another poisonous substance in *Amanita phalloides*, a toxalbumin like pulegon and thujon, to explain the poisoning from this fungus. He brought forward no evidence whatever to substantiate this view and with our present knowledge of the subject we should accept the *Amanita toxin* as the active principle, the *Amanita hemolysin* (phallin of Kobert) playing but a subsidiary rôle if it acts at all in cases of poisoning in man. Whether the gastro-intestinal irritation resulting in the excessive vomiting and diarrhea is due to the action of the *Amanita toxin* or whether some other substance operating especially upon the mucous membranes of the alimentary canal is present in the fungus is not yet definitely established.

AMANITA MUSCARIA LINNÆUS

The poisonous properties of *Amanita muscaria* have been known from early times, and among the fungi recognized as deadly to man on ingestion this fungus was included with *Amanita phalloides* by the earliest writers. The use of a decoction made from it as a fly poison has led to its common name "fly agaric." The peculiar effects which follow its ingestion in which excitement, delirium, and hallucinations are produced by small, non-fatal doses, has led to its employment by the peasants of Siberia to induce a kind of drunkenness, in orgies of which the participants are said to have swallowed the urine of those under its effects in order to bring on the intoxication. (See George Kennan⁴). Deaths in these orgies produced by drinking decoctions of the "fly amanita" were by no means rare among the Koraks. Poisoning from ingestion of the fungus on the belief in its edibility has been observed for many years and cases have been reported by Forster,⁵ Cagliéri,⁶ Prentiss,⁷ and many others, including Orfila,⁸ Mautner,⁹ Paulet,¹⁰ Gillot,¹¹ Boyer,¹² and Sartory.¹³ While the symptoms are violent and alarming, the mortality

¹ Rabe, Zeitschr. f. exp. Path. u. Ther., 1911, ix, 2.

² Ford and Brush, Jour. Pharm. and Exp. Ther., 1914, vi, 195.

³ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, Bd. ii.

⁴ G. Kennan, Tent Life in Siberia, new ed., 1910, p. 198.

⁵ Forster, Boston Med. and Surg. Jour., 1890, 125, 267.

⁶ Cagliéri, Med. Record, New York, 1897, 52, 298.

⁷ Prentiss, Phila. Med. Jour., 1898, 2, 607-611.

⁸ Orfila, Traité de Toxicologie, Paris, 1845.

⁹ Mautner, Allg. wien. med. Zeit., 1861, No. 8, p. 61.

¹⁰ Paulet, Traité des champignons de France, 1793.

¹¹ Gillot, Étude médicale sur l'empoisonnement par les champignons, Lyon, 1900.

¹² Boyer, Jour. de Méd. de Bordeaux, 1909, p. 235.

¹³ Sartory, Rev. de med. leg., Paris, 1911, xviii, 133-135.

is not high. Thus Gillot¹ reported 21 cases, with no death. Roch² added 23 more cases, also with no mortality. More recently Kobert³ reported 34 cases of poisoning from *Amanita regalis* (Königfliegenpilz) all of whom recovered. Fatal cases have been reported however by Cagliéri⁴ and by Prentiss.⁵

Botanical Features.—The best description of *Amanita muscaria* is given by Farlow,⁶ which we quote in full.

"The fly agaric (*Amanita muscaria*), so called because decoctions of it are used for killing flies, is in most places, at least in the northern and eastern parts of the country, a common species—often a good deal more abundant than the common mushroom. It is found during the summer along roadsides, on the borders of fields, and especially in groves of coniferous trees. It prefers a poor soil, of gravelly or sandy character, and occurs only exceptionally in the grassy pastures preferred by the common mushroom. It grows singly and not in groups, and attains a large size, being one of the most striking toadstools. It differs from the common mushroom in having gills which are always white, never pink or purple, and in having a



FIG. 75.—*Amanita muscaria* (one-half natural size).

hollow stem which is bulbous at the base and clothed with irregular, fringy scales on all the lower part. The pileus varies in color from a brilliant yellow to orange and a deep red, the yellow and orange being more frequent than the red. The surface is polished (and sometimes sticky), having scattered over it a larger or smaller number of prominent, angular warty scales, which can be easily scraped off. The gills and stalk are white, and there is a large membranous collar, which hangs down from the upper part of the stem.⁷ The close resemblance of *Amanita muscaria* to certain edible amanitas, in particular to *Amanita caesaria*, one of the most highly prized edible mushrooms has led to many cases of poisoning. This is particularly true among the foreign-born inhabitants of America who mistake the poisonous

¹ Gillot, Étude médicale sur l'empoisonnement par les champignons, Lyon, 1900.

² M. Roch, Les empoisonnements par les champignons, Geneva, 1913.

³ Kobert, Deutsch. Arch. f. klin. Med., 1918, Bd. exxvi, 47-75.

⁴ Cagliéri, Med. Record, New York, 1897, 52, 298.

⁵ Prentiss, Phila. Med. Jour., 1898, 2, 607-611.

⁶ Farlow, Some Edible and Poisonous Fungi, Bulletin 15, U. S. Dept. of Ag., Div. of Veg. Phys., and Path., 1898.

Amanita muscaria of this country for the edible *Amanita cæsaria* of Europe. The *Amanita cæsaria* of Europe is apt to have a yellowish color and the *Amanita muscaria* a reddish brown, while the *Amanita muscaria* in America is usually yellow and the *Amanita cæsaria* reddish brown.

Clinical Symptoms.—The symptoms of poisoning by *Amanita muscaria* are so striking and characteristic as to lead to an early accurate diagnosis. Almost immediately following its ingestion, sometimes in one or two hours, and usually in five or six, the patients begin to show an excessive salivation, perspiration, and laceration accompanying a violent retching and vomiting, with a profuse diarrhea with watery stools. The pulse is slow and irregular, the respirations accelerated, and the patients dyspneic, the bronchi being filled with mucus. Mental symptoms come on rapidly, giddiness with confusion of ideas and rarely hallucination. There is a great variation in the intensity of the different symptoms, sometimes the gastro-intestinal disturbance being the most prominent, at other times the mental and nervous symptoms predominating. When small quantities of the fungus are eaten the symptoms may be very mild, consisting of an excessive salivation and perspiration with a vague feeling of discomfort and uneasiness in the stomach and bowels, the symptoms subsiding spontaneously in a few hours. In more severe cases the vomiting and diarrhea may be so excessive at the start as to rid the alimentary canal of the offending material, after which the mental and nervous symptoms become the prominent feature. Finally when large quantities of the fungus are eaten the nervous and mental manifestations may be seen in the early stages of poisoning, the patients showing delirium, violent convulsions, and an early loss of consciousness from which they cannot be roused; or the patient may retain consciousness only to die from paralysis of respiration. Finally, in certain cases after a preliminary attack of nausea, vomiting, and diarrhea, excessive perspiration and salivation, the patients sink into a deep sleep which lasts several hours from which they wake profoundly prostrated, but on the road to recovery. In nearly all cases of *Amanita muscaria* intoxication the pupils are contracted and fail to react to light and accommodation. The condition of the pupils is important and should always be observed carefully since they furnish an important aid to the correct diagnosis. In mild cases of poisoning by *Amanita muscaria* and in severe cases properly treated the prognosis is good, the patients being restored rapidly to normal health. There are apparently no cases of chronic intoxication such as are seen with *Amanita phalloides*. It is also important to note that many specimens of *Amanita muscaria* have a bitter taste, so that only small quantities of the fungus are eaten. The occurrence of renal glycosuria and nephritis in cases of poisoning from fungi thought to be *Amanita muscaria* has been noted by Alexander.

ILLUSTRATIVE CASES

A very striking instance of poisoning by *Amanita muscaria* has been reported by Prentiss,¹ which is characteristic and so illustrates the usual course of events that

¹ Prentiss, Phila. Med. Jour., 1898, 2, 607-611.

it may be described in full. The Count de Vecchi, attached to the Italian legation in Washington and thoroughly familiar with the edible and poisonous fungi in Italy, purchased a considerable quantity of mushrooms on the street near one of the public markets in Washington. These mushrooms he evidently regarded as an edible species such as *Amanita caesaria*. At breakfast the following morning the Count and his physician, Dr. K., ate the cooked fungi in considerable quantity, noticing their agreeable and even delicious flavor. The breakfast was finished about half-past eight and within fifteen minutes the Count felt symptoms of serious illness. At nine o'clock he was found by his family lying prostrate on his bed oppressed by the fear of impending death. He developed blindness, trismus, difficulty in swallowing and early lost consciousness. Terrible convulsions then supervened, of such a violent character as to break the bed upon which he was lying. Despite the administration of apomorphin and atropin, the Count never recovered from his coma and died on the second day. His physician, Dr. K. on returning to his office immediately after breakfast, soon began to be dizzy and to suffer from double vision and other ocular symptoms. He quickly lapsed into unconsciousness, in which state, he remained for five hours, with one or two intervals of lucidity. Under treatment with apomorphin and atropin recovery set in about seven o'clock in the evening. His restoration to health was complete, the physician living for many years after this experience. These two cases represent the extremes of "muscaria" intoxication: on the one hand, the profound depression of the nervous system resulting in death within forty-eight hours, and on the other, the rapid amelioration of symptoms without permanent lesions.

Characteristic non-fatal cases of *Amanita muscaria* intoxication have been described by Boyer¹ who observed five individuals who were poisoned by eating cooked specimens of *Amanita muscaria*. All showed the characteristic symptoms and all recovered. It is interesting to note that in one instance a cat fed portions of the cooked "muscaria" died with symptoms of muscarin-poisoning. Sartory² also reported the poisoning of one individual who ate *Amanita muscaria*, showed the usual symptoms and recovered. According to Hockauf³ the death of a cat from eating cooked *Amanita muscaria* was reported in 1872 by Wutcher,⁴ and Roch⁵ refers to the instances reported by Gillot⁶ of a young dog which died from eating the l'amanite fousse-orange (*A. muscaria*).

Pathologic Findings.—There have been but few autopsies upon individuals dead of *Amanita muscaria* intoxication and we know little or nothing about the lesions found in man. It is stated however that the heart is greatly dilated and that there are no degenerative changes such as are characteristic of *Amanita phalloides* poisoning. In small animals treated with subcutaneous doses of decoctions of this fungus there is little to be seen beyond an intense congestion of the alimentary canal with hemorrhages into the stomach and intestines. These hemorrhages are due to small ulcers in the wall of the gut and suggest that the poisonous constituent of the "fly agaric" may be eliminated through the mucous membrane. The degenerative changes in the internal organs with the deposition of fat so characteristic of "phalloides" intoxication are absent in "muscaria" intoxication in animals.

The Active Principle of Amanita Muscaria.—The active principle of the "fly agaric" was obtained from the plant by Schmeideberg and Koppe⁷ in 1869 and named by them *Muskarin*. The fungi are first carefully cleaned and extracted with alcohol, then precipitated

¹ Boyer, Jour. de Méd. de Bordeaux, 1909, p. 235.

² Sartory, Rev. de med. leg., Paris, 1911, xviii, 133-135.

³ Hockauf, Wien. klin. Wchnschr., 1904, 17, 731.

⁴ Wutcher, Wien. klin. Presse, 1872.

⁵ M. Roch, Les empoisonnements par les champignons, Geneva, 1913.

⁶ X. Gillot, Bull. trim. de la Soc. Mycol. de France, 1902, xviii, 384.

⁷ Schmiedeberg and Koppe, Das Muskarin, Leipzig, 1869.

with lead acetate for the removal of impurities. The filtrate, after freeing from alcohol, is taken up in water and shaken with animal charcoal. It is now neutralized or made slightly acid and precipitated with mercury-potassium-iodid, by preference a concentrated solution containing an excess of mercuric iodid. The precipitate formed is pressed out between filter-paper and decomposed by hydrochloric acid. A compound, muscarin-hydrochlorid, is formed, which on drying over sulphuric acid gives crystals of needles and prisms. (See Kunkel.¹) According to Harnack² the final preparation in which the crystals of muscarin-hydrochlorid appear contains also an inactive base which he named *amanitin* and which is probably cholin or bilineurin. The muscarin salt is the more easily soluble and can be removed by filtration.

The method of Harmsen,³ which is employed more generally at the present time than the older methods, consists of treating 100 grams of the finely chopped fresh fungi several weeks with 96 per cent. alcohol, filtering, and evaporating over the water-bath to a syrup. This syrup, dark brown in color, is repeatedly treated with alcohol and evaporated, being eventually mixed with sand and dried several days in a desiccator. This dried material is now extracted with absolute alcohol, evaporated on the water-bath, taken up in water, and warmed till the alcohol disappears. A slight precipitate appears in this solution, consisting of oily brown masses and a turbidity. On filtering through a Berkefeld filter the clear yellow neutral fluid is taken up in 100 c.c. of water so that 1 c.c. of solution corresponds to 1 gram fresh fungi. It is finally freed from the atropin-like base (Pilz-atropin) by making weakly alkaline with sodium carbonate and repeatedly shaking with ether. After neutralization with dilute hydrochloric acid and removing the ether by evaporation it is ready for use.

Muscarin was first regarded as an alkaloid by Schmiedeberg and Koppe.⁴ It was also prepared synthetically by the oxidation of cholin. It had the empiric formula $C_5H_{15}NO_3$. It has now been shown by a number of investigators that it is probably an ammonia derivative and that there are at least five similar substances having the same formula, but varying in their effect on the animal organism (see Zellner⁵ and Kobert⁶).

Muscarin is present in the fungus in relatively small amount. It is, however, extremely active and persists for a long time in the dried plant. Its pharmacologic action has been studied extensively and is now well understood. It acts directly upon the sympathetic or autonomic nervous symptom, producing an increased secretion from the various glands of the body by its stimulation of the terminal filaments

¹ Kunkel, Handbuch der Toxikologie, 1901.

² Harnack, Arch. f. exp. Path. u. Pharm., 1875, 40, 168.

³ Harmsen, Arch. f. exp. Path. u. Pharm., 1903, 50, 361. Quoted from Fahrig, Ibid., 1920, Bd. 88, 227.

⁴ Schmiedeberg and Koppe, Das Muskarin, Leipzig, 1869.

⁵ Zellner, Chemie der höheren Pilze, Leipzig, 1907.

⁶ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, ii, 1224.

of the secretory nerves and a paralysis of the heart and respiration by a corresponding stimulation of the inhibitory nerve endings of the vagus nerve. Atropin, by its depressing action upon the same nerves which muscarin stimulates, is a perfect physiologic antidote for muscarin and also for synthetic muscarin, which may be prepared by the oxidation of cholin. The presence of muscarin in suspected materials may easily be demonstrated on the frog's heart. Applications of small quantities to the cardiac muscle produce an immediate stopping of the heart in diastole. This is quickly overcome by the application of a dilute solution of atropin. After the frog's heart is again contracting and dilating normally further applications of muscarin have no effect. Muscarin was also found by Schmiedeberg¹ in specimens of *Amanita muscaria* gathered in the Caucasus, and there can be little doubt that the peculiar effects exhibited by the peasants who use it as a decoction to induce drunkenness are due to this substance. Schmiedeberg² subsequently obtained another principle from the Siberian *Amanita muscaria* which acts like atropin, producing a dilatation of the pupils. This he named *Muscaridin*. Its presence in greater or less amount in *Amanita muscaria* would, according to Schmiedeberg, neutralize or offset the action of the muscarin and thus explain the relative immunity of the Koraks to fatal poisoning by *Amanita muscaria*. The substance *Muscaridin* was renamed "Pilz-atropin" by Kobert.³ Finally, Harmsen⁴ has shown that extracts of *Amanita muscaria* are twice as toxic weight for weight as pure muscarin and contain a poison which produces in animals long-continued convulsions with a fatal outcome, this effect not being neutralized by atropin. This substance was named "Pilztoxin" by Harmsen. Further investigation is needed to determine more definitely the presence of this toxic substance in *Amanita muscaria* and its relation to fatal cases of poisoning by the "fly agaric" such as have been reported by Cagliéri⁵ and others. Here 3 children, aged five, eight, and ten years, ate small quantities of *Amanita muscaria*. They developed the characteristic nervous symptoms and despite the liberal use of atropin died in thirty hours.

AMANITA PANTHERINA DE CANDOLLE

Amanita pantherina closely resembles *Amanita muscaria*, differing from it chiefly in size and color. It is seldom found in America, but may be represented here by Alkinson's *Amanita cothurnata*. *Amanita pantherina* is a common amanita in Europe, particularly in France and Germany. In these countries it is recognized as a deadly poisonous species, and Boehm⁶ has isolated muscarin from it. *Amanita pantherina* is frequently the cause of poisoning in which delirium and

¹ Schmiedeberg, See Harnack, Arch. f. exp. Path. u. Pharm., 1875, iv, 168-190.

² Schmiedeberg, Arch. f. exp. Path. u. Pharm., 1881, xiv, 376.

³ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, ii, 1224.

⁴ Harmsen, Arch. f. exp. Path. u. Pharm., 1903, 50, 361. Quoted from Fahrig., Ibid., 1920, Bd. 88, 227.

⁵ Cagliéri, Med. Record, New York, 1897, 52, 298.

⁶ Boehm, Arch. f. exp. Path. u. Pharm., 1885, 19, 60.

hallucinations with visions of beautiful vari-colored objects predominate over the gastro-intestinal symptoms. This type of poisoning resembles the muscaria drunkenness in Siberia, and it is said that the plant is used in Japan to induce intoxication. Inoko¹ has isolated muscarin from the Japanese *Amanita pantherina* and has also found in it a substance like the "Pilz-atropin" of *Amanita muscaria*.

Cases of poisoning by *Amanita pantherina* are not very common in Europe, but Gillot² in 1900 reported 30 cases. The illness was not serious and only 2 fatalities resulted. More recently Louvriot³ observed the poisoning of 5 individuals who ate a meal of fungi thought to be *Amanita rubescens*, but later shown to be *Amanita pantherina*. About seven hours after eating the fungi symptoms of poisoning came on. They consisted of vomiting, diarrhea, thirst, headache, and precordial pain. Three individuals, a man of forty-two, a man of thirty-four, and a child of eight years, died in about fifty hours, a woman and another child recovering. *Amanita pantherina* is included in Raschke's⁴ tables of poisonous and suspicious species as *Amanita umbrina*, and marked "pileus poisonous."

OTHER POISONOUS AMANITAS

A number of other amanitas are deadly poisonous, their properties being identical with those of *Amanita phalloides*. The most important of these is *Amanita verna*, the young form of *Amanita phalloides*, often called the "destroying angel" of Bulliard. Others, like *Amanita virosa*, Fries, *Amanita sprete*, Peck, *Amanita phalloides*, variety *citrina* (often called *Amanita citrina*), have long been recognized as poisonous by mycologists, and Ford⁵ has shown that they contain the same poisonous principles as the *phalloides*. In addition to these species a number of others have been regarded as "suspicious" for some time. These fungi have been shown by Ford to be intensely poisonous to animals apparently containing the *Amanita toxin*. They should all be classed as "deadly poisonous." The most important of these are *Amanita porphyria*, Albertini and Schweinitz, *Amanita strobiliformis*, Vittadini, *Amanita radicata*, Peck, *Amanita chlorinosma*, Peck, *Amanita mappa* (Batsch), Fries, *Amanita morrisii*, Peck, *Amanita citrina*, Persoon, and *Amanita crenulata*, Peck. The closely related species, *Amanitopsis volvata* (Peck), Saccardo, should be included in the same group. While the majority of amanitas are poisonous, several species are known to be edible including the beautiful *Amanita caesaria*. Other probably edible amanitas are *Amanita rubescens*, Fries, *Amanita junquillea*, Quelet, *Amanita solitaria*, Bulliard, and *Amanita russuloides*, Peck. *Amanita frostiana* was first described by Peck as a minor variety of *Amanita muscaria*, which it closely resembles. Specimens examined on several occasions by Ford contained no poisonous principles. All these so-called edible amanitas should be sedulously avoided by any but the most expert mycologist.

THE BOLETI

The Boleti are tube-bearing fungi belonging to the group Polyporaceæ which grow in the woods and fields, some of them to a large size. They are often 6 to 8 inches in height with a pileus 5 to 6 inches in diameter. They have thick stems and tops containing a good deal of fleshy material. Many of the boleti are highly prized for food and *Boletus edulis*, Bulliard, is employed very largely in France and Italy

¹ Inoko, Mittheil. a. d. Med. Fac. d. k. Jap. Univ., Tokio, 1887-89, i, 227-306.

² Gillot, Étude medicale sur l'empoisonnement par les champignons, Lyon, 1900.

³ V. Louvriot, Rev. méd. de l'est., Nancy, 1903, xxv, 727-730.

⁴ W. Raschke, Naturgeschichtliche Tafeln, No. 1, Tafel giftiger und verdächtiger Pilze.

⁵ Ford, Jour. Pharm. and Exp. Ther., 1910, i, 275; 1911, ii, 285; Ford and Brush, Ibid., 1914, vi, 191.

and in Germany, where it is known as the "Steinpilz." Several species are poisonous. Thus Boehm¹ has isolated muscarin from *Boletus luridus* Schaeffer, and Utz² has obtained a basic substance named boletin from *Boletus satanas*, Lenz. Boletin is probably identical with muscarin. Neither of these species are especially common in America and cases of poisoning from them have not been described. Collins,³ however, reported in 1899 the poisoning of 5 individuals from the ingestion of *Boletus miniato-olivaceus*, Schaeffer, variety *sensibilis*, Frost. The symptoms came on in about two hours in 2 persons who ate freely of the cooked fungi and consisted of vomiting, purging, chilly sensations and prostration with narrowing of the field of vision. In one instance recovery was complete by the next morning, but the other individual collapsed. After injections of ether and brandy he revived, but did not recover normal health for two or three weeks. Three other people ate sparingly of the mushrooms and experienced the same sensations, but of milder grade, recovering completely.

A number of boleti have been examined for toxicity by Ford⁴ and Ford and Sherrick.⁵ *Boletus miniato-olivaceus*, variety *sensibilis*, is poisonous to guinea-pigs, killing them after a progressive emaciation. It apparently does not contain muscarin. *Boletus felleus*, Bulliard, which has an intense and lasting bitter taste and is usually avoided by mycologists, is poisonous to both rabbits and guinea-pigs, producing a chronic cachexia, but not containing muscarin. *Boletus chromapes*, Frost, regarded by McIlvaine as an edible species, is also poisonous to small animals. In general, the poisonous boleti have a disagreeable taste, in consequence of which they are not eaten in sufficient quantity to cause serious illness.

The other boleti examined including *Boletus clintonianus*, Peck, *Boletus caripes*, Kalchbrenner, *Boletus paluster*, Peck, *Boletus chrysenteron*, Fries, *Boletus affinis*, Peck, *Boletus ornatipes*, Peck, *Boletus bicolor*, Peck, *Boletus separans*, Peck, *Boletus ravanellii*, Berkeley and Curtis, and *Boletus rozanæ*, Frost, were free from poisonous principles.

Boletus felleus, Bulliard, and *Boletus pachypus*, Fries, are regarded by Kobert⁶ as poisonous, and Raschke⁷ includes these species with *Boletus piperatus*, Bulliard, which has a bitter taste, in his chart of poisonous and suspicious mushrooms.

THE CHANTERELES

The chanterelles include several edible species, *Cantharellus cibarius*, Fries, being widely employed in Germany, where it is known as the Pfifferling, and in Austria, where it is called the Rötling. According to most of the German mycologists *Cantharellus aurantiacus* (Wulf), Fries, is a poisonous species. Roch⁸ has recently reported the death of a person in Geneva in 1916, with symptoms of diarrhea and vomiting, from the ingestion of decayed chanterelles.

THE CLITOCYBES

Two species of clitocybe are poisonous, *Clitocybe illudens*, Schweinitz, and *Clitocybe dealbata*, Sowerby, variety *sudorifica*, Peck. *Clitocybe illudens* is a very large fungus of a bright orange-brown color growing in clumps at the bases of tree trunks. It has a characteristic phosphorescent glow at night in consequence of which it is often called "Jack o' lantern" or "will of the wisp." Cases of non-fatal poisoning from its use as food have long been known, but the plant has a disagreeable taste and is not often eaten.

Typical cases of poisoning by *Clitocybe illudens* (*Agaricus illudens*) were reported by Farlow⁹ in 1897. Four individuals ate rather sparingly of this fungus and in about two hours were taken with violent, free and vigorous vomiting, which lasted all the afternoon, with no special pain, discomfort, or diarrhea. The action of the

¹ Boehm, Arch. f. exp. Path. u. Pharm., 1885, 19, 60.

² Utz, Apoth. Zeit., 1905, xx, 993.

³ Collins, Rhodora, 1899, i, 21.

⁴ Ford, Jour. Pharm. and Exp. Ther., 1911, ii, 285. Also Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, iv, 321.

⁵ Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1911, ii, 549.

⁶ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, Bd. ii.

⁷ W. Raschke, Naturgeschichtliche Tafeln, No. 1, Tafel giftiger und verdächtiger Pilze.

⁸ Roch, Rev. méd. de la Suisse Rom., Geneva, 1917, xxxvii, 253-270.

⁹ Farlow, Rhodora, 1899, i, 43.

fungus was that of a very simple and painless emetic. The next day the patients were entirely well. Farlow also refers to an instance in the Institution for the Deaf and Dumb at Morgantown, North Carolina, where "eight teachers and children were poisoned very badly" from eating the same fungus. All suffered from the characteristic terrible nausea and all recovered. Fischer¹ has recorded 29 cases of *Clitocybe illudens* poisoning in Detroit.

Ford² has pointed out that extracts of *Clitocybe illudens* are poisonous to animals, producing an acute intoxication in guinea-pigs, the toxic properties being sometimes destroyed by boiling. Clark and Smith³ have shown that extracts of *Clitocybe illudens* produce a characteristic muscarin effect when applied to the exposed frog's heart, this being relieved by atropin. This fungus thus contains a poison closely related to muscarin.

According to Peck⁴ *Clitocybe dealbata*, Sowerby, variety *sudorifica*, Peck, produces on ingestion an intense perspiration and a mild feeling of discomfort. Ford and Sherrick⁵ have shown that this species contains a peculiar poison whose properties are similar to those of muscarin but not definitely identical with it. Roberts⁶ has recently observed the poisoning of two individuals, a man and wife, from eating cooked specimens of this fungus. The man ate about 16 specimens in the evening and in half an hour he began to have profuse perspiration and difficulty of vision, with contracted pupils. This was followed by diarrhea, twitching of the arms and legs, a feeling of exhilaration, and scantiness of urine. On treatment with emetics, purgatives, and atropin, he recovered by the next morning, except for a loss of the sense of taste and a scantiness of saliva. The woman ate 8 specimens and experienced similar symptoms with pain in the top of the head. She was quite well the next day.

In a case recently reported to the author by letter, a man ate a large meal of the plants and experienced a most profuse perspiration without other symptoms of poisoning.

Similar poisoning of 3 individuals from a closely related species, *Clitocybe morbiifera*, has been reported by Fischer⁷ and Ichimura,⁸ has recently stated that *Clitocybe acromelalga*, nov. sp., is slightly poisonous on ingestion.

THE COPRINUS

The majority of coprinus species are edible and one, *Coprinus comatus*, Fries, the "shaggy mane" or "horse-tail" mushroom, which grows prolifically on lawns in late summer and in the autumn, is a great favorite. Other edible species are *Coprinus atramentarius* (Bulliard), Fries, and *Coprinus micaceus* (Bulliard), Fries. One form, *Coprinus narcoticus*, Batch, is said by Kobert⁹ to be poisonous and by Massee¹⁰ to have a very strong and unpleasant smell.

THE CORTINARIAS

One species of cortinarius, *Cortinarius traganus*, Fries, is regarded as poisonous by Raschke.¹¹ Stevenson¹² states that this cortinarius has a very fetid odor, the name being derived from the Latin "tragus," a goat.

THE ENTOLOMAS

The entolomas are rather small fungi with angular rose-colored spores. They are seldom, if ever, the cause of poisoning in America. *Entoloma sinuatum*, Fries, has

¹ Fischer, Agaricaceæ of Michigan, Publication 26, Biological Series 5. Michigan Geological and Biological Survey, December, 1918.

² Ford, Jour. Pharm. and Exp. Ther., 1911, ii, 285. Also Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, ii, 321.

³ Clark and Smith, Mycologia, 1913, v, 224.

⁴ Peck, Report of the State Botanist, New York State Museum Bulletin, 1911, No. 150, 53.

⁵ Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1911, ii, 549.

⁶ Roberts, Mycologia, 1912, xiii, 42-44.

⁷ Fischer, Agaricaceæ of Michigan, Publication 26, Biological Series 5. Michigan Geological and Biological Survey, December, 1918.

⁸ Ichimura, Bot. Gaz., 1918, 65, 109-111.

⁹ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, Bd. ii.

¹⁰ Massee, British Fungi, London, p. 349.

¹¹ W. Raschke, Naturgeschichtliche, Tafeln, No. 1, Tafel giftiger und verdächtiger Pilze.

¹² Stevenson, British Fungi. 1886.

long been regarded as poisonous on the authority of Worthington Smith.¹ *Entoloma lividum*, Bulliard, is an important cause of mushroom-poisoning in France, ranking next to *Amanita phalloides* in certain years in point of frequency. Thus Sartory² (quoted from Roch³) states that 66 cases of poisoning from *Entoloma lividum* occurred in France in 1912, with 1 death, in a child of four years, and 26 cases in France in 1913. Sartory describes an entolomian syndrome (syndrome entolomién) consisting of:

Rapid onset within a half to two hours after ingestion.

Violent symptoms at onset.

Vomiting.

Diarrhea.

Syncope.

Periods of remission.

Pupillary changes.

Excessive thirst.

Dry mouth so that patient cannot speak.

No disturbance of intelligence.

Recovery.

Sartory states that only 2 deaths from poisoning by *Entoloma lividum* are known to him. Labesse,⁴ in his report on mushroom-poisoning in Maine-et-Loire in France for the year 1912, includes a number of non-fatal cases from *Entoloma lividum*, and Roch,⁵ in his series reported for Geneva in 1916, gives 32 cases of poisoning from fungi identified as *Entoloma lividum* and 17 more due probably to this form.

Several species of entoloma were found poisonous to small animals by Ford,⁶ including *Entoloma sinuatum*, Fries, *Entoloma strictius*, Peck, *Entoloma nidorosum*, Fries, *Entoloma salmoneum*, Peck, *Entoloma cuspidatum*, Peck, and *Entoloma rhodopolium*, Fries.

HELVELLA OR GYROMYTRA ESCULENTA

For many years poisoning, often severe and fatal, has been reported from Germany and Austria from the consumption of false morels or lorchells. According to Kobert⁷ there are no authentic cases of poisoning from the true morels, of which he recognizes 5 edible species. He has reported over 160 recorded cases of poisoning from the false morels variously called *Helvella esculenta* and *Gyromytra esculenta*. The active principle of this poisonous fungus was isolated by Boehm and Külz⁸ in 1885, who named it Helvellic acid. It is a hemolytic substance, acid in reaction, with the empiric formula $C_{12}H_{20}O_7$. It had previously been shown by Boström⁹ and Ponfick¹⁰ that the poisonous principles in *Helvella esculenta* were completely soluble in hot water, the aqueous extract killing dogs when given by the stomach, while the residue left after extraction was quite harmless. The symptoms of intoxication in these animals were the same as when they were given the fresh fungus by mouth and in both instances there was marked hemoglobinuria, pointing to a hemolytic intoxication. According to both Boström and Ponfick, the toxicity of *Helvella esculenta* disappears or is much lessened when the fungi are dried. Helvellic acid, as obtained by Boehm and Külz, is also toxic to dogs when given by mouth, likewise producing hemoglobinuria, and there can be little doubt that it is the active principle of *Helvella esculenta*.

Typical cases of *helvella* or lorchell poisoning have been recorded by Hockauf¹¹ and by Lövegren.¹² In Hockauf's cases the fungi eaten were identified by the Austrian Health Department (Kreisgericht) as *Helvella esculenta*, Persoon, or *Hel-*

¹ Worthington Smith, See Stevenson, p. 192.

² A. Sartory, Bull. des Scien. pharm., Mars-Avril, 1915, xxii, 68.

³ Roch, Rev. méd. de la Suisse Rom., Geneva, 1917, xxxvii, 253-270.

⁴ Labesse, Anjou méd., 1913, xx, 276.

⁵ Roch, Rev. méd. de la Suisse Rom., Geneva, 1917, xxxvii, 253-270.

⁶ Ford, Jour. Pharm. and Exp. Ther., 1911, ii, 285. Also Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, ii, 321.

⁷ Kobert, Münch. med. Wehnschr., 1917, 44, 1041. Also Lehrbuch der Intoxikationen, 1906.

⁸ Boehm and Külz, Arch. f. exp. Path. u. Pharm., 1885, xix, 403.

⁹ Boström, Deutsch. Arch. f. klin. Med., 1886, 32, 209. Also Sitzungsberichte der physikalischmedizinischen Societät zu Erlangen, June, 1880.

¹⁰ Ponfick, Virchow's Archiv, 1882, 88, 445.

¹¹ Hockauf, Wien. klin. Wehnschr., 1905, xviii, 1058.

¹² Lövegren, Jahrb. f. Kinderheilk., 1909, Bd. xix, 412-421.

vella suspecta, Krombholz. Four children were taken sick in the morning after a meal of fungi taken the day before. Relieved temporarily by emetics, they were again, in the evening, seized with violent cramps in the abdomen. One child of nine years died the next morning, twenty-four hours after eating the fungi. Autopsy showed a catarrh of the stomach. Another child, aged ten years, barely survived, suffering for several days with catarrh of the stomach. Two older children, aged fifteen and seventeen years, recovered rapidly. Hockauf was unable to poison dogs or cats with cooked specimens of the same fungi as were eaten by the children, and suggested that the plants, which are well known to be poisonous to young children when eaten raw, had not been cooked. This could not be verified. In Lövegren's report, 5 individuals were poisoned from eating fungi identified as *Helvella esculenta* (Steinmorcheln). One of these, a child of five years, died in fifty-three hours. She was taken sick four hours after eating the mushrooms with vomiting, pain in the abdomen, lassitude, tonic cramps in the neck and extremities, widely dilated pupils, jaundice, weak pulse, slow, irregular respiration ending in coma and death. At autopsy there were hemorrhages in the mucous membrane of the stomach and in the internal organs, the liver showed parenchymatous degeneration and pigmentation, the spleen an excessive pigmentation. All the autopsy findings pointed to a hemolytic intoxication. One other individual, the maid servant, was seriously ill, also with jaundice, but recovered in about a week.

These two reports are in agreement with previous investigations which indicate that the source of morell-poisoning is the false morell, or lorchell. Umber,¹ however, described 3 instances of poisoning from true morells. In the first, 3 individuals ate a soup from the first washings (Kochwasser) of fresh morells purchased in the market. Seven hours after, one of these individuals, a girl of twenty-six years, was taken violently ill with vomiting, fainting, and marked jaundice. The pupils were normal, but in the evening the patient was delirious. Liver and spleen were swollen. The following day she was better and on the second day quite recovered. The jaundice was slow to abate. One other individual had an attack of vomiting, the third remaining well. In the second instance, 5 individuals ate a meal of morells and later a soup made from the first wash-water. Some hours later 3 became violently ill with vomiting and pain in abdomen. There was no diarrhea. Jaundice came on in forty hours. All recovered. In the third instance a girl of twenty-six years ate a dish of morells including, the first wash-water. Seven hours later she was taken ill with the same symptoms, including jaundice. Liver and spleen were swollen. She also recovered. Umber's cases, as well as that of Henius² in 1916, are in line with the general opinion in Germany and Austria that the true morells as well as the false morells may at times be poisonous, especially if they are eaten with the first water in which they are washed. It is usually stated in these countries that the morells should not be eaten raw and that the first water in which they are cooked should be thrown away. Indeed, in some of the German descriptions of edible fungi, as in Raschke's charts,³ both the true morells and the false morells (helvellas) are so described. In 1916 Lyon⁴ described an instance of poisoning which indicates some of the difficulties of this question. Here 2 individuals were poisoned from eating unidentified fungi thought to be the edible pffiferling, *Cantharelles cibarius* (Gelbling), and possibly mistaken for the *Cantharelles aurantiacus* (the false Gelbling). The fungi were eaten in the evening by a man and his wife who had purchased them in the market. On the day after the meal the man was ill with a feeling of coldness and chills, recovering the following day. On the second day after the meal the woman became quite sick, suffering from pain in the stomach and vomiting. The next day she was jaundiced and her abdominal pains had increased. She then showed an extensive subcutaneous rash and the urine became coffee brown in color. These symptoms continued, with paralysis of the right facial nerve, ptosis of the left lid, dilatation of the pupils, poor vision, and exophthalmos, with a slow pulse 52 to 54 a minute. Finally, opisthotonos and coma developed, the patient dying ten days after eating the fungi. The clinical diagnosis was *meningitis* and *hemoglobinuria* or *methemoglobinuria*. At autopsy there was a thrombosis of the longitudinal sinus and of the vessels of the pia mater, and a massive destruction of a portion of the brain substance from an extensive hemorrhage. The kidney showed hemosiderosis and a chronic interstitial nephritis. There was an accumulation of brownish-yellow pigment not giving iron reactions in the liver, with some fat

¹ Umber, Deutsch. med. Wchnschr., 1916, 42, 627.

² Henius, Ibid., 1916, 42, 701.

³ W. Raschke, Naturgeschichtliche Tafeln, No. 1, Tafel essbarer Pilze.

⁴ E. Lyon, Med. Klin. Berl., 1916, xii, 237-263.

in the liver cells; the spleen was enlarged and showed the same type of pigmentation. Chemical analysis of the kidney revealed a total of 1.36 gram of iron in the 2 organs. All the pathologic lesions in the case pointed to a true hemolytic intoxication and the author regards the case as one of poisoning from the false morels or helvellas. This is the first autopsy on this type of poisoning in which modern methods of pathologic examination were employed and clearly establishes the picture of hemolytic intoxication, which is quite different from that seen in poisoning by the amanitas. More recently two papers on false morell-poisoning have been published where the lesions were studied with great care. Stahl, in 1918, reported the poisoning of 6 individuals from eating lorchells (*Helvella esculenta*). Of these, 3 individuals showed only mild symptoms of vomiting and jaundice, recovering completely in a few days. One patient had the usual symptoms and a low hemoglobin as well, also recovering. Another patient had wide dilatation of the pupils, jaundice, and unconsciousness, also recovering completely in about five weeks. His urine showed evidences of hemolysis—shadows of red blood-corpuscles. The sixth case, a man of forty years, developed jaundice and unconsciousness, dying in forty-eight hours after eating the fungi. At autopsy there was universal jaundice, subpleural and subepicardial hemorrhages, an enlargement of the spleen, a fatty degeneration of the heart muscle, a fatty infiltration and a deposition of iron pigment in the epithelial cells of the kidney, and a hemosiderosis of the liver. The author regards these cases as typical of poisoning by the lorchells or false morels and suggests that the urobilinuria which the cases exhibited was produced by the same type of blood destruction which would result in hemoglobinuria in dogs.

In 1918 Herzog¹ described 4 non-fatal cases of lorchell-poisoning and 1 fatal case. In the 4 non-fatal cases all the patients showed transient jaundice—recovering completely in a few days. In the fatal case a soldier ate 2 liters of morels he had gathered himself, pouring off the first cooking water. The following day he showed vomiting, jaundice, anemia, emaciation of face, and great weakness. The pulse was faint and the patient complained of a burning sensation in the stomach. Death occurred forty-eight hours after eating the fungi. At autopsy there was icterus, a high-grade fatty degeneration of heart, liver, and kidneys with hemorrhages in pleura, epicardium, mediastinum, and bone-marrow. Marked hemosiderosis in both liver and kidneys was demonstrated. The bone-marrow showed many erythroblasts and iron pigment (pigment colored blue with potassium ferrocyanid). The author concludes that the icterus is hematogenous in origin and that the lesions are quite different from those in *Amanita phalloides* intoxication.

Finally in 1918 Kobert² stated that 1 death and several cases of poisoning from *Helvella esculenta* had occurred in Rostock in 1917 and another death and several cases in Rostock in 1918. Kobert also states that Dittrich³ collected over 40 cases of helvella poisoning, with 4 deaths, from the literature of 1916, chiefly in the Kurland. The only cases of poisoning by *Helvella esculenta* in America were reported by Dearness⁴ who says that a family was poisoned in London, Ontario, with 1 death, and by Fischer,⁵ who records 2 non-fatal cases in Michigan.

From these various observations on this type of poisoning it is clear that the majority of cases have been traced to the consumption of the false morels, *Helvella esculenta* or *Gyromytra esculenta*, and that it is a true hemolytic intoxication. Whether the true morels, *Morella esculenta*, are also poisonous is not entirely clear, since the differentiation between the morels and the helvellas is somewhat difficult. The fact that morels are eaten in many areas in Germany without untoward results suggests that they are either not poisonous at all or that they contain poisonous principles easily given up to hot water.

An examination of American examples of *Helvella* or *Gyromytra esculenta* was made by Ford and Sherrick⁶ in 1913, who found that the specimens which had been collected by Mr. Simon Davis at Stow, Massachusetts, did not contain poisons of any description, hemolytic or otherwise. Another specimen of *Morchella esculenta*, however, was found poisonous to guinea-pigs by Ford, the toxicity disappearing on drying the fungi.

¹ Frank Herzog, Ztschr. f. Path. Wiesb., 1918, 21, 297-320.

² Kobert, Deutsch. Arch. f. klin. Med., 1918, exxvi, 47-75.

³ Dittrich, Ber. d. deutsch bot. Gesellsch., 1916, Bd. 34, H. 9.

⁴ John Dearness, Mycologia, 1911, iii, 75.

⁵ Fischer, Agaricacæ of Michigan, Publication 26, Biological Series 5. Michigan Geological and Biological Survey, December, 1918.

⁶ Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, iv, 321.

THE HEBELOMAS

The hebelomas are rather small agarics with clay-colored spores. Two species, *Hebeloma rimosum*, Fries, and *Hebeloma fastibile*, Fries, are recognized in Germany as very poisonous. (See Kobert.)¹ *Hebeloma crustuliniforme* (Bulliard), Fries, is said to have a bitter taste and is regarded as a poisonous species in Europe. (See Stevenson.)² According to Swanton,³ who also regards this species as poisonous, it is named from the resemblance of its pileus to a small pie (*Lt. crustulum*) and is said to have the nickname "poison pie."

THE HYGROPHORI

The hygrophori are white-spored agarics usually regarded as edible. One species, *Hygrophorus conicus* (Scopoli), Fries, is in bad repute among mycologists, and Demange⁴ has reported the poisoning of 6 people in China from the ingestion of a fungus thought to be identical with the form found in Europe. Of the 6 persons affected, 4 died and 2 recovered. The symptoms were not unlike those seen in *Amanita phalloides* intoxication.

Specimens of this species gathered in America were found poisonous to guinea-pigs by Ford,⁵ producing a fatal cachexia. Several other species of hygrophori, including *Hygrophorus pratensis* (Persoon), Fries, variety *cinereus*, *Hygrophorus pratensis*, variety *albus*, and *Hygrophorus marginatus*, Peck, exhibited a similar toxicity.

THE HYPHOLOMAS

The hypholomas are fairly large mushrooms with purplish-brown spores, several species of which are edible. In Europe *Hypholoma sublateralium*, Schaeffer, is regarded as poisonous (see Atkinson⁶) and is said to have a bitter taste. Kobert states that *Hypholoma fasciculare*, Hudson, the "falsche Stockschwamm," is not edible, while Kunkel⁷ says the same species may be poisonous, but not very; that it has a bitter taste and is thus not eaten. It is included in Raschke's tables⁸ of poisonous and suspicious species. *Hypholoma fasciculare* is frequently called the "sulphur-top" because of its yellow color. Specimens of *Hypholoma instratum*, Britzelmayer, and *Hypholoma cernua*, Müller (*Psilocybe cernua* (Wahl), Fries), were both found acutely poisonous to guinea-pigs by Ford.⁹

THE INOCYBES

The inocybes are small yellowish-brown plants about 2 inches in height with spores which vary in color from yellowish brown (Murrill) or pale brown (Massee) to red (Atkinson). The genus has assumed considerable importance recently because of the very careful botanic work upon it by American collectors, especially Simon Davis,¹⁰ and because of the poisonous properties of several of its members. Apparently the first case of poisoning from inocybes was reported by Murrill.¹¹ The mushrooms were cooked and eaten in the middle of the day by 4 individuals and tasted by 3 others. In the 4 people who ate the fungi in some quantity symptoms varying in severity came on in about half an hour. They consisted of a sensation of fulness in the head, rapid action of the heart, profuse perspiration, abdominal distress with nausea, and slight mental confusion with dizziness. In the 3 individuals who tasted the mushrooms but 1 felt the effects, a slight nausea. The species was identified as *Inocybe infida* (Peck), Earle. Subsequently Clark and

¹ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, Bd. ii.

² Stevenson, British Fungi, 1886.

³ E. W. Swanton, Fungi and How to Know Them, London, 1909, p. 127.

⁴ Demange, Bull. del a Soc. mycol. de France, 1906, September, Fasc. 15.

⁵ Ford, Jour. Pharm. and Exp. Ther., 1911, ii, 285. Also Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, ii, 321.

⁶ Atkinson, Mushrooms, New York, 1903, p. 26.

⁷ Kunkel, Handbuch der Toxikologie, 1901, ii, 1055.

⁸ W. Raschke, Naturgeschichtliche, Tafeln, No. 1, Tafel giftiger und verdächtiger Pilze.

⁹ Ford, Jour. Pharm. and Exp. Ther., 1911, ii, 285. Also Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, iv, 321.

¹⁰ Simon Davis, Rhodora, 1911, xiii, 57; 1914, xvi, 45.

¹¹ Murrill, Mycologia, 1909, i, 211.

Kantor¹ isolated from this species a poisonous principle which closely resembled muscarin in its effect on animals, this effect being neutralized by atropin. A little later Ford² demonstrated that *Inocybe infelix*. Peck, is poisonous to both rabbits and guinea-pigs, the effects resembling but being not quite identical with symptoms produced by extracts of *Amanita muscaria*. It has also been shown by Ford and Sherrick³ that *Inocybe decipiens*, Bresadola, contains a poison belonging to the muscarin-pilocarpin series, and by Ford⁴ that *Inocybe maxima*, Davis, contains substances acting on animals like *Amanita muscaria*, these being neutralized by atropin. Recently Fahrigh⁵ has reported 3 cases of poisoning from the ingestion of cooked mushrooms identified by Söhmer as a new species and named by von Ricken *Inocybe lateraria* (Ziegelroter Risspilz). The patients felt generally uncomfortable in the night after eating the mushrooms, suffering from abdominal distress, salivation, sweating, disturbances of the accommodation of the eye, chills, and diarrhea. Complete recovery set in after two to three days. From specimens of the same fungus Fahrigh obtained, by the method recommended by Harmsen⁶ for the extraction of muscarin from *Amanita muscaria*, a purified solution giving the characteristic reaction of muscarin on frogs and cats, being neutralized by atropin. According to Fahrigh a fatal case of inocybe-poisoning was reported by Dittrich⁷ in 1916, the fungi being identified as *Inocybe frumentacca*, Bulliard (Weinroter Risspilz). In this instance the plants were tasted by 1 individual and eaten in considerable quantity by 2 others. The first person suffered from transient sweating, dizziness, and discomfort. Of the 2 who ate the mushrooms, 1 exhibited severe symptoms, but recovered after vomiting, while the other showed violent abdominal pain and cramps, with blindness, dying fifteen hours after eating the fungi. Dittrich⁸ has also reported 2 severe cases of poisoning from *Inocybe repanda*, Fries, and Hermann⁹ a case from *Inocybe sambucina*, Fries. It is evident that several different species of inocybes contain muscarin or substances closely resembling it and that all varieties should be carefully avoided.

THE LACTARIUM

Lactarius torminosus, Fries, has long been known by mycologists to produce painful gastro-intestinal disorders. It is a fairly large mushroom with white spores, exuding a milky juice on breaking. Characteristic cases of poisoning were reported by Goldman¹⁰ in 1901, who observed 11 cases. The symptoms were vomiting, diarrhea, pain in the abdomen, irregular pulse, and a general condition of intoxication not unlike that seen in "muscaria" poisoning. Three of the patients died. At autopsy no special lesions could be found beyond a fatty liver. Gillot¹¹ states that *Lactarius torminosus* is a drastic purgative. Kobert reports that it is eaten in East Russia, and Bulliard¹² says that it is very astringent, but is eaten in Russia when preserved in salt and eaten with oil and vinegar. It has been shown by Ford¹³ that extracts of *Lactarius torminosus* produce an acute death in both rabbits and guinea-pigs, the symptoms being a little like those seen from *Amanita muscaria*, but without convulsions. Extracts boiled half an hour had no toxicity, as previously reported by Kunkel,¹⁴ and plants cooked in the method described for eating them were also free from poisonous action. It has also been shown by Ford that *Lactarius uvidus*, Fries, which is usually regarded as poisonous (Kunkel and Kobert), is actually toxic to guinea-pigs. *Lactarius rufus*, Scopoli, and *Lactarius necator*,

¹ Clark and Kantor, Mycologia, 1911, iii, 175.

² Ford, Loc. cit.

³ Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, iv, 321.

⁴ Loc. cit.

⁵ Fahrigh, Arch. f. exp. Path. u. Pharm., 1920, lxxxviii, 227-246.

⁶ Harmsen, Arch. f. exp. Path. u. Pharm., 1903, 50, 361. Quoted from Fahrigh, Ibid., 1920, 88, 227.

⁷ Dittrich, Ber. d. deutsch. bot. Gesellsch., 1916, Bd. 34.

⁸ Dittrich, Ibid., 1918, Bd. 36.

⁹ Hermann, Der Pilz-urd Kräuterfreund, 1919, Bd. iii, Heft 1.

¹⁰ Goldman, Wien. klin. Wchnschr., 1901, xiv, No. 12, 279.

¹¹ Gillot, See McIlvaine and Macaddam, One Thousand American Fungi, 1900, p. 163.

¹² Bulliard, See McIlvaine and Macaddam, One Thousand American Fungi, 1900, p. 163.

¹³ Ford, Jour. Pharm. and Exp. Ther., 1911, ii, 285. Also Ford and Sherrick, Jour. Pharm. and Exp. Ther., 1913, ii, 321.

¹⁴ Kunkel, Handbuch der Toxikologie, 1901, ii, 1055.

Persoon, are included by Raschke¹ in his chart of poisonous and suspicious mushrooms. Kobert regards the latter species as poisonous, calling it the "Mordschwamm." Many of the lactarii are edible, including the favorite, *Lactarius deliciosus*, Fries.

THE LEPIOTAS

The majority of the white-spored lepiotas are edible, especially the very large and beautiful *Lepiota procera*, Scopoli, the parasol mushroom. One American species, *Lepiota morgani*, Peck, which is especially abundant in the Ohio valley, is poisonous. The first case of poisoning from this species is probably that of Blount,² who states that one individual ate a small piece as large as the little finger about 5 o'clock one evening. In an hour he was seriously ill with vomiting and diarrhea with profuse, painless, watery stools. Another individual ate two portions the size of a pea and swallowed the juice of two other portions of the same size. The taste was pleasant, but excited loathing. Immediate discomfort followed ingestion of the mushroom, and within an hour violent vomiting set in, occurring every five to ten minutes and lasting for two hours. The next day this individual had a profuse diarrhea. Both recovered completely under the administration of stimulants. According to Chestnut,³ *Lepiota morgani* is a frequent cause of serious illness and is responsible for at least 1 death. Specimens of this species gathered in the District of Columbia were found by Chestnut to be poisonous to small animals, the toxic properties being destroyed by heating. Hollis Webster⁴ has reported an instance in which an entire family ate *Lepiota morgani* for supper and were all violently ill within two hours. All recovered.

Lepiota morgani is one of the most beautiful of American agarics. It is even larger than *Lepiota procera*, for which it is usually mistaken. It is distinguished from the parasol mushroom by its green spores among other characteristics.

According to Dearnese,⁵ *Lepiota naucinoides*, Peck, usually regarded as edible may cause transient illness. The "naucinoides" may be identical with *Lepiota naucina* which has been reported poisonous to several individuals by Krieger.⁶

THE PANÆOLI

The panæoli are black-spored agarics, of which one species, *Panaeolus retirugis*, Fries, is a very beautiful plant growing abundantly on lawns, especially when heavily manured. It is edible, having a rather nutty flavor and odor. This species is usually avoided because of its close resemblance to a poisonous form, *Panaeolus papilionaceus*, Fries. *Panaeolus papilionaceus* has long been known to produce a peculiar condition of excitement and hilarity. A typical instance of panæolus-poisoning was reported in 1914 by Vernill.⁷ In this instance 2 individuals ate *Panaeolus papilionaceus* (probably mistaken for *Panaeolus retirugis*) and symptoms of poisoning came on in twenty minutes. The persons suffered from mental confusion with hilarity and disturbances of vision, lasting only a few hours and followed by complete recovery. No gastro-intestinal disturbance.

In 2 cases of poisoning known to the writer similar symptoms appeared about three hours after eating the mushrooms. The symptoms began to subside in about six hours and the patients were entirely well the next morning.

A more serious instance of panæolus-poisoning has been reported by Murrill.⁸ Here 5 persons ate black-spored agarics which appeared in a mushroom bed seeded with *Agaricus campestris* spawn. The symptoms of distress came on almost immediately after eating the mushrooms and consisted of great prostration with drawn faces and very widely dilated pupils not reacting to light or accommodation, cardiac and respiratory depression, and a feeling of numbness and tingling in the feet and legs. There was no nausea or vomiting. One of the individuals was profoundly prostrated, only recovering when the attending physician injected strophanthin directly into the heart muscle. All recovered. The species responsible

¹ W. Raschke, Naturgeschichtliche, Tafeln, No. 1, Tafel giftiger und verdächtiger Pilze.

² Blount, Medical Record, 1901, xxvi, 815.

³ Chestnut, Asa Gray Bulletin, 1900, 8, 87-93.

⁴ Hollis Webster, Rhodora, 1915, xvii, 30.

⁵ John Dearnese, Mycologia, 1911, iii, 75.

⁶ Personal communication.

⁷ A. E. Vernill, Science, 1914, n. s., xi, 408-410.

⁸ Murrill, Mycologia, 1916, viii, No. 3, 186.

for these cases is regarded by Murrill¹ as a new one, being described by him as *Panaeolus venenosus*. This identification has not been accepted by Flora Patterson,² of the Department of Agriculture in Washington, who regards the mushroom as *Panaeolus papilionaceus*.

In some unpublished experiments by the present writer with this fungus it was found that it contains a peculiar poison which stops the frog's heart in a short time, the action not being neutralized by atropin. *Panaeolus retirugis* was poisonous to guinea-pigs on subcutaneous inoculation (Ford³). *Panaeolus campanulatus*, Fries, is also poisonous on ingestion according to Krieger.⁴

THE PHALLOIDEÆ

Several species of the phalloideæ are reported to be poisonous to animals on ingestion, the most important being *Ityphallus impudicus*, Linnæus, variety *imperialis*. This is a nasty, foul-smelling plant growing to a height of 4 to 5 inches and is commonly called the "stinkhorn." It is said to be the cause of extensive poisoning of swine, but little information is available in regard to its poisonous properties. Specimens of *Ityphallus impudicus* examined by the writer were free from poisonous principles. According to Masee,⁵ *Clathrus cancellatus*, Linnæus, has properties similar to those of *Phallus impudicus*, and Farlow⁶ states that *Clathrus columnatus*, Bosc, is poisonous to swine. Both these plants bear a superficial resemblance to *Phallus impudicus*.

THE PLEUROTİ

Most species of the genus pleurotus are edible. Farlow,⁷ however, states that *Pleurotus olearius* (*Agaricus olearius*, Persoon) is poisonous when eaten, resembling *Clitocybe illudens*, and producing nausea, vomiting, and purging. This species grows especially in Southern Europe. According to Fischer⁸ it causes poisoning in France like that from *Clitocybe illudens*.

THE PHOLIOTİ

The pholioti are ferruginous or ferruginous-brown agarics, of which one species, *Pholiota autumnalis*, Peck, has been reported by Peck⁹ as deadly poisonous. Three individuals, a mother and 2 children, living in Minnesota, were seized with violent symptoms resembling those seen in *Amanita phalloides* intoxication after eating *Pholiota autumnalis*. The 2 children died, but the mother recovered. Specimens of this species gathered in New York State were examined by Ford and Sherrick¹⁰ and found to be quite as poisonous to both rabbits and guinea-pigs as *Amanita phalloides*. The lesions resembled markedly the lesions seen in "phalloides" intoxication in animals. *Pholiota autumnalis* should be regarded as deadly poisonous.

POLYPORUS OFFICINALIS

Polyporus officinalis, Fries, is the source of a therapeutic principle, *agaricinic acid*, $C_{14}H_{27}OH(COOH)_2$, which is employed to lessen excessive perspiration. Large doses cause vomiting and purging by their irritating action on the mucous membranes.

THE RUSSULAS

Many species of the white-spored russulas are edible, but one or two being poisonous. The brilliant red *Russula emetica*, Fries, has long been known to cause serious gas-

¹ Murrill, *Edible and Poisonous Mushrooms*, New York, 1916, p. 59.

² See Warning to Mushroom Growers, published by the Office of Information, U. S. Department of Agriculture in 1916.

³ Ford, *Jour. Pharm. and Exp. Ther.*, 1910, i, 275; 1911, ii, 285; Ford and Brush, *Ibid.*, 1914, vi, 191.

⁴ Krieger, *Mycologia*, 1911, iii, 200.

⁵ Masee, *British Fungi*, London, p. 349.

⁶ Farlow, *Bot. Gaz.*, 1890, xv, 45, 46.

⁷ Farlow, *Rhodora*, 1899, i, 43.

⁸ Fischer, *Agaricaceæ of Michigan*, Publication 26, Biological Series 5. Michigan Geological and Biological Survey, December, 1918.

⁹ Peck, *Bulletin of the New York State Museum*, No. 157, p. 9.

¹⁰ Ford and Sherrick, *Jour. Pharm. and Exp. Ther.*, 1913, iv, 321.

tro-intestinal disturbance with violent vomiting. Roch¹ in 1917 reported the poisoning of 8 individuals from eating a mixture of *Russula emetica* and *Russula sardonica*. All suffered from diarrhea and vomiting, but all recovered. Frey² in 1912 reported the poisoning of 3 individuals, a father and 2 sons aged twelve and fourteen years, from the consumption of fungi identified as a species of *russula* by Fischer, Director of the Botanical Institute at Basle. The father ate sparingly of the fungi, but the children ate them on two occasions. Both boys were taken violently ill with vomiting and diarrhea. The twelve-year-old boy died in five days of nephritis, the autopsy revealing jaundice, hemorrhages in the serous membranes, in the stomach and intestines and in the mesenteric glands, edema of the brain, and nephritis. The fourteen-year-old boy died in four days of acute hemorrhagic nephritis, showing at autopsy hemorrhages in the serous membranes, erosion of the stomach, nephritis, and a fatty liver. Kobert³ has isolated 3 basic substances from *Russula emetica*, cholin, muscarin and, "Pilz-atropin." *Russula foetens*, Fries, along with *Russula emetica* and *Russula fragilis*, Fries, is included by Raschke⁴ in his table of poisonous and suspicious species.

THE SCLERODERMAS

According to Kobert⁵ and Raschke⁶ *Scleroderma vulgare*, Fries (*Scleroderma aurantiacum*, Bulliard), is poisonous. This form is usually known in Germany and Austria as "false truffles."

THE TRICHOLOMAS

The European authors regard some of the tricholomas as poisonous. Thus Roch⁷ reports 7 cases of non-fatal poisoning from "tricholomes avariés," decayed tricholomas, with symptoms of vomiting and colic. In 1920 Sartory⁸ tested *Tricholoma tigrinum*, Schröter (same as *Tricholoma pardinum*, Quelet), and found that guinea-pigs were killed five hours after ingestion. He regarded the species as having a toxicity like that of *Entoloma lividum*. In America Fischer⁹ has reported the poisoning of 7 individuals from a tricholoma recognized as a new species by Atkinson and named *Tricholoma venenatum*. The symptoms came on about one hour after ingestion of the fungi and consisted of vomiting, sometimes bloody, and retching with prostration in 3 individuals. No deaths.

THE VOLVARIA

A number of species of the rose-spored volvaria are regarded as edible by American authors such as *Volvaria bombycina* (Persoon), Fries, and *Volvaria speciosa*, Fries, by Atkinson,¹⁰ and *Volvaria maritimus*, Peck (*Agaricus maritimus*), by Peck.¹¹ The French mycologist Chauvet¹² regards all the volvaria as poisonous. Roch¹³ also considers some of the species as poisonous, particularly *Volvaria gloicephala*, de Candolle quoting the cases reported by Chanel and Clerc,¹⁴ who state that a woman of twenty-five died in twenty-four hours after eating a mixture of different fungi containing *Volvaria gloicephala* and *Laccaria laccata*. She showed vomiting bilious in character, diarrhea, violent colic, great pain in the region of the kidney, and excessive thirst. Her father, aged sixty-three, and mother, aged fifty-seven years, were severely poisoned at the same time but recovered. Sartory¹⁵ regards *Volvaria*

¹ Roch, Rev. méd. de la Suisse Rom., Geneva, 1917, xxxvii, 253-270.

² W. Frey, Zeitschr. f. klin. Med., Berlin, 1912, lxxv, 455-471.

³ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, Bd. ii.

⁴ W. Raschke, Naturgeschichtliche, Tafeln, No. 1, Tafel giftiger und verdächtiger Pilze.

⁵ Kobert, Lehrbuch der Intoxikationen, 2d ed., 1906, Bd. ii.

⁶ W. Raschke, Naturgeschichtliche, Tafeln, No. 1, Tafel giftiger und verdächtiger Pilze.

⁷ Roch, Rev. méd. de la Suisse Rom., Geneva, 1917, xxxvii, 253-270.

⁸ A. Sartory, Bull. Acad. de Med., Paris, 1920, 3 s., lxxxiii, 76-78.

⁹ Fischer, Agaricaceæ of Michigan, Publication 26, Biological Series 5. Michigan Geological and Biological Survey, December, 1918.

¹⁰ Atkinson, Mushrooms, New York, 1903, p. 26.

¹¹ Peck, Bulletin Torrey Botanical Club, 1899, 26, 67.

¹² S. Chauvet, Gaz. d. hôp., Paris, 1912, lxxxv, 1499-1504.

¹³ M. Roch, Les empoisonnements par les champignons, Geneva, 1913.

¹⁴ Chanel and Clerc, Bull. de la Soc. des Naturalistes de l'Ain, 1904, p. 22.

¹⁵ A. Sartory, Les empoisonnements par les champignons (été de, 1912), Paris, 1912. Quoted from Roch.

gloicephala as poisonous. Stevenson¹ says that the smell of this species is strong and unpleasant, its taste disagreeable, and that it is very poisonous according to Letellier.

Gillot, according to Roch,² states that *Volvaria speciosa*, Fries, is responsible for several cases of poisoning, with 6 deaths, among them that of a man and his fiancée who partook of them at a dinner given in their honor.

The American examples of this species are usually regarded as edible (Atkinson).

CLASSIFICATION OF TYPES OF MUSHROOM-POISONING

We are now in possession of a considerable body of knowledge concerning the species of mushrooms which are poisonous to man on ingestion or which are poisonous to animals on inoculation. The lesions produced by them have been studied with great care as well as the physiologic effects upon the nervous system. The number of definitely poisonous species has been increased greatly by recent investigations, and there are nearly eighty plants about which our information has gradually become more exact. Some species produce their poisonous effects by acting directly upon the cells of the internal organs; others, by their stimulation of the terminal filaments of the nerve-fibers; others, by their gastro-intestinal irritation, and still others, by an action upon the nerve centers. In many instances the poisonous mushrooms have several effects, producing gastro-intestinal and nerve symptoms or the gastro-intestinal disturbance together with degenerative changes in the cells. Indeed, all the poisonous mushrooms cause more or less violent disturbances of the alimentary canal, but our knowledge as to whether this is due to the various poisons found in the fungi or to some other principle with an irritant action on the gastro-intestinal mucosa is by no means satisfactory. The most widely accepted classification of mushroom-poisoning is that of Huseman,³ who distinguished three types, as *mycetismus intestinalis*, *mycetismus choleriformis*, and *mycetismus cerebrealis*. The intestinalis mycetismus is due to an acute gastro-intestinal inflammation produced by such species as *Boletus satanas*, *Russula emetica*, and *Lactarius torminosus*. The choleriform mycetismus shows violent vomiting and diarrhea, with collapse, delirium, and coma, and is due to *Amanita phalloides* and *Helvella esculenta*. The third form, the cerebral mycetismus, is due to *Amanita muscaria* and *Amanita pantherina*, but depends upon the "Pilz-atropin" present in these fungi and not upon the muscarin. It is evident that the classification of Huseman rests upon somewhat antiquated knowledge of the poisons in mushrooms and contains a number of fundamental errors. Thus the poisoning from *Amanita phalloides* can easily be differentiated now from that due to *Helvella esculenta* both on clinical and pathologic evidence, while the intoxication following ingestion of *Amanita muscaria* and *Amanita pantherina* is almost surely due primarily to muscarin and not to "Pilz-atropin." We suggest the follow-

¹ Stevenson, British Fungi, 1886.

² M. Roch, Les empoisonnements par les champignons, Geneva, 1913.

³ Huseman, See Boudier-Huseman, Die Pilze in ökonomischer, chemischer und toxikologischer Hinsicht, Berlin, 1867.

ing classification of mycetismus (mushroom-poisoning) as being more in accord with modern knowledge of this field.

1. **Mycetismus Gastro-intestinalis.**—Here the symptoms are mainly violent nausea and diarrhea usually transient in character. There are seldom fatalities. The principal species producing it are *Russula emetica*, *Boletus satanas*, *Boletus miniato-olivaceus*, *Lactarius torminosus*, *Entoloma lividum*, and *Lepiota morgani*.

2. **Mycetismus Choleriformis.**—Here the symptoms are gastro-intestinal at the outset and are followed by rapid loss of strength and weight, violent paroxysms of pain, nephritis and anuria, delirium, and coma. The mortality is high, at least half the poisoned individuals dying. The species producing this type are *Amanita phalloides* and its varieties, the closely related white amanitas, *Pholiota autumnalis* and *Hypophorus conicus*.

3. **Mycetismus Nervosus.**—Here violent gastro-intestinal symptoms predominate at the outset, but these are accompanied by profuse perspiration and salivation, delirium and hallucinations, convulsions and coma. While the victims are seriously ill the symptoms are apt to subside rapidly. Deaths are rare but not unknown. Many mild cases of poisoning also occur, with merely vomiting and diarrhea or profuse perspiration and salivation. The fungi producing this type of mycetismus are only the species containing muscarin or closely related substances and include *Amanita muscaria*, *Amanita pantherina*, *Clitocybe illudens*, *Clitocybe sudorifica*, *Inocybe infelix*, *Inocybe infida*, *Inocybe lateraria*, *Inocybe sambucina*, *Inocybe frumentacea*, and *Inocybe repanda*. (Poisoning from *Russula emetica*, *Boletus luridus*, and *Boletus satanas* may eventually be put in this group.)

4. **Mycetismus Sanguinareus.**—Here the preliminary symptoms are gastro-intestinal, but jaundice and anemia rapidly develop with coffee-brown urine (hemoglobinuria). The mortality is low. The only species definitely responsible for this type of mycetismus is *Helvella esculenta*, which contains a resistant hemolytic poison. *Morchella esculenta* may also contain such a poison but this is not definitely determined.

5. **Mycetismus Cerebralis.**—In this type of mycetismus the symptoms are cerebral in character and consist of transient excitement and hallucinations. The pupils are widely dilated and the patient may collapse. Recovery is the rule. But 2 species, *Panæolus papilionaceus* and *Panæolus campanulatus* have thus far been shown to produce this condition. It is possible that *Coprinus narcoticus* may also cause similar symptoms.

TREATMENT

In all cases of mushroom intoxication, it is desirable to discover as early as possible the particular poisonous fungus which has been eaten. In many instances, specimens of the plants may be obtained and accurately identified. In other instances, the description given by the victims will suffice to enable one to recognize the species ingested.

Occasionally the vomitus or the stools contain bits of fungi which may be recognized, and sometimes the spores may be found and submitted to an expert mycologist for examination. To some extent the treatment and to a large extent the prognosis depend upon the particular type of poisonous mushroom which has been taken. However, while the identification of the species is of great importance, yet it must be remembered that many cases are so severe and require such vigorous and prompt treatment that there is little time for such investigations. Moreover, it is a difficult matter, even in our large cities, to find one capable of differentiating the species from the examination of the spores or bits of fungi found in the vomitus or feces. As has been indicated already, the symptoms of the various types of poisoning are so characteristic that the expert physician who has expert knowledge of the subject will have no great difficulty in establishing his diagnosis.

General Measures.—In all cases of mushroom-poisoning, whatever be the type, it is essential that the stomach and bowels be emptied as soon and as completely as possible, in order to remove portions of the fungi remaining in these organs. It is true that vomiting and purging may be prominent symptoms of the poisoning, but this may not clear the gastro-intestinal tract sufficiently to prevent later absorption of the toxic principles. Hence, gastric lavage and high enemata should be given early, the washing being continued until no further solid material is shown in the wash fluid. Further, it would seem advisable to give at once atropin subcutaneously and even intravenously if the symptoms are urgent. While atropin is of special value in poisoning with the muscaria, yet it will do no harm in cases of phalloides intoxication and, hence, may be administered before an exact diagnosis of the type of poisoning has been made.

Amanita Phalloides.—In *Amanita phalloides* and similar poisonings the prognosis is always grave and but little can be done, aside from the above measures, beyond the administration of remedies such as the opiates to relieve the intense suffering. It is important to remember that the damage to the kidney and the nephritis, which seems to be regularly present, may be an important cause of the nervous symptoms. Any measures which are applicable to nephritis in general should be employed in these cases. Stimulants, such as strychnin, should be given in periods of collapse and digitalis administered when the heart action is weak. Charcoal may be given by mouth to absorb the poison, as recommended by Professor Maheu.¹ There may be some value in the injections of oxygen, Hubert² having used with good results the injection of 300 to 350 c.c. into the muscular tissue of the thigh twice daily for a period of three days and then once daily for three days. The so-called Focheur method of fixation in which subcutaneous abscesses are produced to combine with the poison is bad therapy.³

¹ J. Maheu, *Med. Press and Circ.*, London, U. S., lxxxviii, p. 398. (Translation of brief note from French literature.)

² J. Hubert, *Jour. de Méd. de Bordeaux*, 1921, xcii, 47.

³ A. Pic and Martin, *J. F. Lyon méd.*, 1913, cxx, 1310-1314.

In a series of 18 cases treated in the Los Angeles County Hospital, Lacey¹ reports only one death, this case being practically moribund on admission to the hospital. The method followed in these cases was as follows: As soon as the cases were received a gastric lavage of salt solution was given, followed by a thorough washing out of the stomach with not less than 1 quart of a solution of potassium permanganate (which was made by diluting a strong stock solution with plain water until the solution was of a deep pink color). This procedure was repeated at least three times a day and after each gastric lavage with this solution, about 2 or 3 ounces of a saturated solution of magnesium sulphate was left in the stomach. The patients were all very much prostrated on admission, were very weak, had low blood-pressures, and subnormal temperatures, and all carried a great deal of albumin, casts of all varieties, and some blood-cells in their urine. They were fed on a very light nephritic diet and given plenty of water to drink. Between times a Murphy drip, consisting of sodium bicarbonate solution, was kept going as long as the patients were able to retain it.

In all cases of poisoning with "phalloides" it should be constantly borne in mind that the symptoms are due to degenerative lesions of the organs and that treatment may be of little avail. We know now, however, from the recent careful study of the pathology of "phalloides" intoxication, that there is evidence that effort is being made towards repair on the part of the liver, so that recovery seems possible if the damage to the organs is not too great.

Amanita Muscaria.—In *Amanita muscaria* poisoning the symptoms are due to the action of muscarin on the nerve terminals, and atropin is a perfect physiological antidote for muscarin. No particular attempt should be made to relieve the vomiting and diarrhea, which are of value in ridding the alimentary canal of the offending materials. Purgatives should be administered if the stomach and bowels are not completely emptied. Atropin should be given at once and repeatedly, both subcutaneously and, if necessary, intravenously. Stimulants, such as strychnia, digitalis, and strophanthus, are also indicated. The treatment of Lacey, as outlined above, should prove of value in this as in other types of mushroom-poisoning.

As far as we know there are no lesions in the internal organs in "muscaria" intoxication. The outlook for recovery is thus excellent if the patient can be tided over the period of acute muscarin-poisoning. In all other cases in which the species ingested contains poisons belonging to the muscarin-pilocarpin series the same line of treatment is indicated as with *Amanita muscaria*. The prognosis in these other cases is good as the poisons, muscarin or similar substances, are present in these plants in very small quantity.

In cases of poisoning in which gastro-intestinal symptoms such as vomiting and diarrhea predominate, as with *Lepiota morgani*, the patient should be watched carefully for signs of collapse which may require energetic treatment by stimulants. In general, the vomiting and the

¹ J. Mark Lacey, Personal communication.

diarrhea subside spontaneously and do not call for remedial measures. Occasionally, however, a gastro-intestinal catarrh may develop requiring careful medication and dieting.

Finally, in cases of poisoning with mental effects alone, as in *pan-æolus* intoxication, the prognosis is always good and the patients need little beyond good purgation. It must always be remembered, in such cases as well as in other mild types of mushroom intoxication, that certain patients may collapse and need energetic stimulation with such drugs as strychnin, digitalis, strophanthus, and alcohol.

We know too little, at the present time, of hemolytic poisoning produced by the *helvellas* or *morells*, and the only line of treatment which might have any rational argument in its favor would be transfusion of blood from a homologous donor. As far as a careful search of the literature goes, this has not been tried.

DISTINCTIONS BETWEEN EDIBLE AND POISONOUS FUNGI

There are no simple rules, such as peeling the top or pileus or cooking with a silver spoon which enable the collector to determine whether mushrooms are edible or poisonous. Certain species contain poisonous principles, while others do not. These poisons bear no relation to the taste of the mushrooms, and many of our most toxic forms have an agreeable and even delicious flavor. Nor does the presence of these toxic ingredients bear any known relation to the soil in which the plants are growing. It is true that the majority of the mushrooms which grow on the lawn or in meadows are edible, and a considerable number of species which grow in the woods are poisonous. The usual belief that mushrooms grow in the fields and toadstools (poisonous mushrooms) grow in the woods has some foundation. There are, however, many poisonous species which occasionally appear on lawns and in fields, and some of the woods mushrooms are edible and contain a good deal of nutrient material. There is but one safe rule for mushroom-eaters. They should study the subject by the aid of good textbooks and learn the distinguishing features of the common edible species.¹ *Only these should be collected and eaten.* In addition, collectors should learn to recognize the poisonous species with certainty. The habit of eating indiscriminately species which are new or not thoroughly familiar to the collector has been responsible for many serious accidents. Well over a thousand species or varieties of mushrooms have been described in America, and while the majority of these are edible, there are over 80 species which are definitely poisonous. Certain groups of mushrooms should be sedulously avoided by any but the most experienced collector. This is especially true of the genus *Amanita*, which includes the mushrooms with the most powerful poisons. All the *Inocybes* should be avoided, since at least eight species are known to be poisonous to man or contain poisonous principles. Care should

¹ Especially valuable for the recognition of the edible mushrooms is Mr. Louis C. C. Krieger's *Common Mushrooms of the United States*, published in the *National Geographic Magazine* in May, 1920.

be exercised in collecting the *Pholioti*, of which one species, *Pholiota autumnalis*, is deadly poisonous on ingestion and contains substances which are highly toxic to animals. Fortunately the number of edible mushrooms is large and it is comparatively easy to learn to recognize them with certainty. The following list contains the species known to be poisonous on ingestion, the species which are poisonous to animals experimentally, and the most important of the forms regarded as poisonous or suspicious by well-known American and European mycologists.

LIST OF POISONOUS AND SUSPICIOUS MUSHROOMS

Amanita phalloides, Bulliard, including *Amanita bulbosa*, Persoon, and its varieties, *alba*, *citrina*, *virescens*, and *olivacea*; *Agaricus bulbosus*, Bulliard; *Amanita venenosa*, Persoon, *Amanita viridis*, Fries; *Amanita porphyria*, Fries, and *Amanita recutita*, Fries; known in older French literature as "l'orange ciguë," "l'orange blanche ou citronée," "l'orange ciguë jaunâtre," and "l'orange souris." In the German literature it is called the "Knollenblätterschwamm" and in the Austrian the "Schierlingspilz." The spring form is usually called *Amanita verna*, but this variety occurs also in the summer and autumn. *Amanita phalloides*, variety *citrina*, one of its varieties, probably does not differ from the *Amanita citrina* of Persoon.

Amanita bisporigera, Atkinson.

Amanita virosa, Fries.

Amanita spreta, Peck.

Amanita porphyria, Albertini and Schweinitz.

Amanita strobiliformis, Vittadini.

Amanita radicata, Peck.

Amanita mappa (Batsch), Fries.

Amanita morrissii, Peck.

Amanita chlorinosma, Peck.

Amanita citrina, Persoon.

Amanita crenulata, Peck.

Amanita muscaria, Linnæus.

Amanita frostiana, Peck. This species may be edible, but so closely resembles

Amanita muscaria that it should not be eaten except by very expert mycologists.

Amanita pantherina (de Candolle), Fries, known also as *Amanita umbrina*.

Amanita cothurnata (Atkinson). (May be same as *Amanita pantherina*.)

Amanitopsis volvata (Peck), Saccardo.

Boletus luridus, Schaeffer.

Boletus satanas, Lenz.

Boletus felleus, Bulliard.

Boletus chromapes, Frost.

Boletus pachypus, Fries.

Boletus piperatus, Bulliard.

Boletus miniato-olivaceus, Schaeffer, variety *sensibilis*, Frost.

Cantharellus aurantiacus (Wulf.), Fries.

Clitocybe illudens, Schweinitz.

Clitocybe dealbata, Sowerby, variety *sudorifica*, Peck.

Clitocybe morbifera, Peck.

Clitocybe acromelalga, Ichimura.

Clathrus cancellatus, Linnæus.

Clathrus columnatus, Bosc.

Coprinus narcoticus, Batsch.

Cortinarius traganus, Peck.

Entoloma nidorosum, Fries.

Entoloma lividum, Bulliard.

Entoloma sinuatum, Fries (*Entoloma fertile*, Berkeley).

Entoloma strictius, Peck.

Entoloma salmoneum, Peck.

Entoloma rhodopolium, Peck.

Entoloma cuspidatum, Peck.

Helvella esculenta, Persoon, also known as *Gyromytra esculenta*.
Hebeloma rimosum, Fries (*Inocybe rimosa*).
Hebeloma fastibile, Fries.
Hebeloma crustuliniforme (Bulliard), Fries (the "poison-pie").
Hygrophorus conicus (Scopoli), Fries.
Hygrophorus pratensis (Persoon), Fries, variety *cinereus*.
Hygrophorus pratensis, variety *albus*.
Hygrophorus marginatus, Peck.
Hypholoma fasciculare, Hudson.
Hypholoma sublateralitium, Schaeffer.
Hypholoma instratum, Britzelmayr.
Hypholoma cernua, Müller (*Psilocybe cernua*).

Inocybe decipiens, Bresadola.
Inocybe infida (Peck), Earle.
Inocybe maxima, Davis.
Inocybe lateraria, von Ricken.
Inocybe frumentacea, Bulliard.
Inocybe infelix, Peck.
Inocybe sambucina, Fries.
Inocybe repanda, Fries.

Lactarius torminosus, Fries.
Lactarius uvidus, Fries.
Lactarius rufus, Scopoli.
Lactarius necatur, Persoon.
Lepiota morgani, Peck.
Lepiota helveola (*Lepiota brunatre*).
Lepiota naucinoides, Peck.
Lepiota naucina, Fries.

Morchella esculenta, Persoon (doubtfully poisonous).

Panaeolus papilionaceus, Fries.
Panaeolus campanulatus, Fries.
Phallus impudicus, Linnæus (*Ityphallus impudicus*, variety *imperialis*).
Pholiota autumnalis, Peck.
Pleurotus olearius, Persoon.
Polyporus officinalis, Fries.

Russula emetica, Fries.
Russula foetens, Fries.
Russula fragilis, Fries.

Scleroderma vulgare, Fries (*Scleroderma aurantiacum*, Bulliard).

Tricholoma tigrinum, Schröter (*Tricholoma pardinum*, Quelet).
Tricholoma venenatum, Atkinson.

Volvaria gloiocephala, de Candolle.
Volvaria speciosa, Fries.

POISONOUS PROTEINS

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IN the first edition of this work (1904) I wrote the section entitled "Ptomaines and Other Bacterial Products in Their Relation to Toxicology." At that time there was considerable testimony to the effect that certain putrefactive products occasionally interfere with the chemical tests for certain alkaloids, and this interference sometimes led to misinterpretation of his findings by the toxicologist. The most important subject I discussed at that time was the possibility of confounding the color tests for morphin with some reactions due to putrefactive products. Within the ten years preceding 1904 two celebrated trials, in which the possibility of mistaking color reactions due to putrefactive products with those indicating the presence of morphin, had occupied the attention of eminent toxicologists both in this country and in Europe. The case of Urbino de Freitas, which occurred in Portugal in 1893, finally involved most of the prominent toxicologists of Europe. Without exception the German experts testified that the evidence of the presence of morphin in the tissues under examination, furnished by the Portuguese chemists, was not sufficient to justify the claims of the latter. Dragendorff, of Russia, and Stevenson, of London, came to the same conclusion. In the Buchanan case in New York, Wolff and I claimed that the color tests for morphin submitted and relied upon by the chemists for the prosecution were not sufficiently convincing to justify the conviction of the accused on this evidence alone. In these 2 cases stress was laid upon the fact, generally recognized, that the amylic alcohol of that time was notably impure and extracts obtained with it from putrefactive tissues occasionally gave color reactions which might be mistaken for those of morphin. I am glad to testify that now (1922) the possible sources of error in mistaking putrefactive reactions for those of morphin have been removed. This improvement has resulted from the greater purity in the extractive reagents used, especially in amylic alcohol, and from the introduction of better analytic methods. I believe that there is now scarcely a possibility that the skilful chemist will have any difficulty in distinguishing between poisonous vegetable alkaloids and protein putrefactive products. It turns out, therefore, that while the article which I wrote for the first edition of this work represented the best information of that time, it is now of historic interest only.

I have been asked by the editors to contribute to this edition a short paper on poisonous proteins. In complying with this request I

wish to state that there is no probability that any of the poisonous proteins will interfere with the chemical tests for either organic or inorganic poisons when properly carried out. I should state with equal emphasis that poisonous proteins are not likely to play any important part in medicolegal investigations; in other words, these substances are not likely to be employed for homicidal purposes. It is true that some of the poisonous proteins are harmful when administered by mouth. Such administration is not with criminal intent, but, as a rule, follows the taking of some infected food, as in cases of botulism. All proteins, be they of bacterial, vegetable, or animal origin, contain a poisonous group, but this group is poisonous only when introduced into the body parenterally and not when taken into the alimentary canal.

My students and I have obtained bacterial proteins, from both pathogenic and non-pathogenic organisms, in amounts sufficiently large to enable us to investigate their chemistry to some satisfactory extent. We have found no bacterial protein which is poisonous to mammals when introduced by the alimentary canal. It should be clearly understood that I am now speaking of the cellular proteins of bacteria and not of their toxins. On the other hand, we have found no bacterial cellular protein which is not harmful when introduced parenterally into mammals. The degree of toxicity manifested by these substances varies greatly, and, as a rule, this variation is in inverse ratio to the infectivity of the living bacterium from which the protein is obtained; in other words, the most infectious bacteria furnish the least toxic protein. The non-pathogenic bacteria supply a more highly poisonous protein than do the pathogenic bacteria. Guinea pigs are highly susceptible to the *Bacillus tuberculosis*, but no amount of the dead cellular substance of this bacillus will kill guinea-pigs; it will produce tubercular nodules in these animals. On the other hand, the guinea-pig is never infected with the *Bacillus prodigiosus*, and yet one part of the protein of this organism to 100,000 parts of the body weight of the guinea-pig will kill when introduced intra-abdominally or intravenously.

The bacterial cellular proteins contain two carbohydrates, one of which is combined with nitrogen and exists as chitin or chitin-like substances in the bacterial cell, while the other carbohydrate is combined with phosphorus and exists in the bacterial cell as a nuclein. Xanthin bases exist in the living bacterial cellular substance in the form of nucleins, and on disruption of the nucleins these bases are set free. Elsewhere I have made the following general statement concerning the composition of bacterial cellular proteins: "We have demonstrated the presence of the following groups among the split products: (a) A chitin-like body consisting of a carbohydrate combined with nitrogen. It seems reasonable to infer that this exists in the cellular substance as a glycoprotein. (b) A carbohydrate group combined with phosphorus from which it is not easily detached. This group reduces copper after prolonged boiling with dilute mineral acid. The amounts as determined by the reduction of Fehling's solution and calculated as

xylose are large, but we are not sure that the reducing substance is all carbohydrate. Indeed, it might be better to speak of both of these groups as those responding to the alpha-naphthol test rather than as carbohydrates and to distinguish between them as non-reducing and reducing bodies. However, it seems clear that the one now under consideration is a subgroup in the nucleinic acid constituent of the cell substance. (c) The presence of nucleinic acid is beyond doubt, as is shown by the high phosphorus content of some of the split products and by the demonstration of the xanthin bases. (d) That one or more protein groups exist in the cell substance. If all these groups exist in the same molecule the cell substance must contain a highly complex molecule which would be best designated as a glyconucleoprotein. The fact that these bodies are removed only by agents capable of causing molecular disruption inclines me to the belief that the molecules which make the cell substance are highly complex. It may be said that this is an assumption and without adequate proof. On the other hand, such a statement as that made by Doerr, that bacterial proteins are of simple molecular structure, is wholly without evidence. Because bacteria are simple morphologically is no proof that they are made up of simple proteins. This certainly is not true even if it should prove that I have overestimated the size of these protein molecules."

The size of the fatal dose of bacterial cellular protein when injected parenterally into mammals varies with the source of the protein, the species of animal, and the fineness to which the poison has been reduced. The coarsely ground cellular protein of the colon bacillus kills guinea-pigs on intraperitoneal injection in doses of 1 to 40,000 parts of body weight. When the same powder is more finely ground it kills all guinea-pigs in a dose of 1 to 75,000 of body weight, and a certain percentage of the animals in doses up to 1 to 2,000,000 parts of body weight.

All bacterial cellular proteins can be split into poisonous and non-poisonous groups. There are various chemical agents which can cause this cleavage. I have generally used a 2 per cent. solution of sodium hydroxid in absolute alcohol. This has the advantage over all other reagents, inasmuch as it not only induces the desirable cleavage, but in part, at least, it separates the poisonous from the non-poisonous group, since the former is freely soluble and the latter insoluble in absolute alcohol. Dilute aqueous alkaline solutions will cleave the bacterial proteins quite as readily as the alcoholic solutions, but in this case both the poisonous and the non-poisonous parts are largely in solution and subsequent separation is difficult. By a similar method, all true proteins can be divided into poisonous and non-poisonous portions. The poisonous group apparently present in all true proteins is freely soluble in absolute alcohol; in fact, more soluble in absolute alcohol than in water. Its aqueous solutions give the Millon test. They do not give the Molisch test, thus showing the absence of carbohydrate. Some of the protein poisons give the Adamkiewicz and Liebermann tests, while

others do not. This test is believed to be due to the presence of tryptophan. The fact that the poisons from certain proteins do not respond to these tests indicates that Doerr's assumption that the poisonous action is due to the presence of this group is without support. The poison gives the Millon test most strikingly and in high dilution. This test is believed to indicate the presence of tyrosin, and it is interesting to note that gelatin, which contains no tyrosin, does not yield the poison. Aqueous solutions are distinctly acid to litmus, and this reaction is due to some organic body. Neutralization with alkalis and alkaline earths weakens the action of the poisons. Poisons from some proteins appear to form definite compounds with calcium and magnesium, and at least some of the calcium bodies are inert. In the dry state the protein poison forms a brownish powder, varying somewhat in shade with the protein from which it is obtained. All preparations have the same marked odor. Whether this substance or these substances should be called proteins or not is a question. Proteins should not be soluble in absolute alcohol. This substance, however, gives the biuret test, and this is generally regarded as the most distinctive test for proteins. Its alcoholic solutions are precipitated by alcoholic solutions of copper, mercury, and platinum. By means of these precipitants, with subsequent removal of the metal with hydrogen sulphid, I have obtained the most potent preparations. By this method we have obtained a body which kills guinea-pigs of from 200 to 300 grams weight in doses of 0.5 milligram given intravenously. The poison is not an alkaloid, although it may possibly be basic in character. As I have stated, the weight of evidence at present is that all true proteins contain a poisonous group; that there is a general similarity in the chemical composition and in the physiologic and toxicologic action, whatever the protein from which the poison is obtained. The protein poison is not likely to concern the toxicologist in his practical work. It is inert when given by the alimentary canal and concerns the practitioner of medicine and the pathologist more than it does the toxicologist.

THE POSTMORTEM IMBIBITION OF POISONS

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IN the first edition of his great work upon toxicology, published in 1845, Orfila speaks as follows on this subject: "It is true that if corrosive sublimate, arsenic, the salts of copper, sulphuric and nitric acid, etc., be introduced into the digestive canal some minutes after death, they induce lesions of tissue resembling up to a certain point those which are developed by the ingestion of these same substances during life. However, it is easy to distinguish these lesions by the following characteristics: (a) In case the poison be introduced after death in solid form, it will be found to exist in large quantity only a short distance beyond the point of its application. Those parts of the digestive canal distant from the point of application, depending more or less upon the length of time intervening between the application and the time of examination, will remain unaltered. While, on the other hand, if it be administered during life, and be not expelled by vomiting or otherwise, it will be widely diffused. (b) If the poison be introduced in solution after death, it will penetrate to a greater distance, but again there will be a notable difference in the extent of its diffusion from that which occurs after its administration during life. (c) When the poison is injected after death there will be a sharp line of demarcation between the tissues penetrated by it and those to which it has not extended. When an irritant poison is introduced during life it causes an inflammation of more or less intensity, which insensibly extends into the adjacent tissue, and there is never a sharp line of demarcation. (d) The redness, the inflammation, the ulceration, and the other lesions are infinitely greater when the poison is introduced during life than when it is applied after death. If, on examination of the cadaver, one finds the rectum or the stomach filled with a large quantity of the poison and the inflammation very slight, one can presume that the poison has been applied after death. (e) There are certain poisons, such as corrosive sublimate and nitric acid, which cause characteristic lesions when injected immediately after death, and it is impossible positively to tell whether these lesions were caused by administration during life, or by application after death. (f) The corrosive poisons, if introduced into the digestive canal twenty-four hours after death, do not develop much redness or inflammation, because they do not extend into the capillaries. (g) These poisons may cause lesions which simulate a mild congestion when they are applied one or two hours after death.

"In all cases of this kind it should not be forgotten that imbibition after death takes place very slowly and will be most marked in parts that are below the point of application. In one case in which the sulphate of copper was introduced into the stomach after death, this salt was found to have penetrated the left side of the diaphragm and the left lung, while the right side of the diaphragm and the right lung did not contain the poison. It will also be found in these cases that in postmortem imbibition the poison does not penetrate to the center of certain organs, or, at least, will be found in greater quantity near the surface. If, however, the examination be not made until after many months and after a time when putrefaction has markedly progressed, it is quite difficult to determine whether the poison was introduced before or after death. In such a case much reliance must be placed upon the symptoms and other evidence of poisoning."

In 1850 Kidd published, in the *Dublin Quarterly Journal of Medical Sciences*, some experiments upon cadaveric imbibition. He injected from 4 to 8 ounces of a solution of arsenic containing 10 grains to the ounce into the bodies of a cat and a rabbit, and found, after about a month, that the poison was widely distributed through the adjacent organs. In the rabbit he found that in this way the poison had penetrated as far as the heart and the tissues of the forelegs.

Kidd's work was so well done and is so applicable to similar cases that have arisen in the last few years that we may with profit quote quite extensively from his communication. He summarizes the evidence in the case as follows:

"Mr. Bleazby, a gentleman of independent fortune, died after an illness of short duration, October 16, 1849. After his death rumors arose that he had been poisoned and an inquest was called for. The body was raised December 15, 1849, and the stomach, liver, and kidneys were removed for examination. The body presented appearances which caused the suspicion that a stomach-pump had been introduced after death, and at the inquest a defense was attempted on the ground that the person had died from natural causes, and that poison had been injected into the stomach afterward." The chemist obtained arsenic from the stomach, and unequivocal evidence of its presence in the liver and kidney. The report of the chemist read as follows: "From the appearance of arsenic in the stomach, kidney, and liver, deponent has no hesitation in stating that in his opinion the death of the individual from whose body these parts were extracted was caused by arsenic. As a matter of opinion, the arsenic must have been received in the stomach before death. It is possible to inject arsenic into the stomach after death, but in that case it could not enter the liver or kidneys; it is only by absorption that it could reach these organs, and absorption ceases immediately after death."

Kidd made not only the experiments already referred to, but, by means of endosmometers, he showed that a solution of arsenic separated from blood-serum by an animal membrane would diffuse until the two fluids were of practically the same composition. Had Kidd's work been

better known, the controversy concerning the diffusion of poisons through the dead body could not have been so sharply contested as it was a few years ago.

In 1852, in a new edition of his work upon toxicology, Orfila reported experiments upon dogs and men. He introduced into the body, through the stomach or rectum, from 30 to 45 grains of arsenic dissolved in a pint of water. The parts of the liver and other organs that lie in contact with the digestive canal were found to contain arsenic, while the other parts were found free from this substance. When the arsenic was introduced into the stomach and the body placed upon the back, the poison was found in the left half of the diaphragm and in the lower lobe of the left lung, while none could be found in the other portions of the diaphragm or in the right lung.

In 1856 three Italians, Moltedo, Ageno, and Granara, published some experiments, of which the following is an abstract: Ten centigrams of arsenious acid was introduced into the empty stomach of a dead rabbit. Twenty-nine hours later analysis showed the presence of arsenic in the lungs, in the walls of the heart, and in the blood. Twenty centigrams was introduced under like conditions into another animal. Seventeen hours later marked arsenical mirrors were obtained from the blood, the lungs, and the heart, and a smaller mirror from the liver. Similar results were obtained in experiments upon another animal into which 7 centigrams of arsenic was introduced twenty-four hours after death, and the analysis was made twenty-four hours later. In the fourth experiment 15 centigrams of arsenic were introduced into the large intestine, and twenty hours later the poison was found in the kidneys and in the urine. In the fifth experiment 30 centigrams were introduced into the stomach of a fetus. After twenty-four hours marked traces of the poison were found in the kidneys. In a sixth case $\frac{1}{2}$ gram of arsenic was introduced into the stomach of a dead boy. Analysis, made a few hours later, failed to show any evidence of diffusion. Finally, a human liver, with the blood-vessels and gall-ducts tied, was allowed to lie for forty hours in an arsenical solution. The examination of a small piece from the center of the liver failed to show the presence of arsenic. They concluded from their experiments that while arsenic may penetrate the blood, lungs, and heart of a dead body, its presence in the interior of the liver is positive proof of its absorption during life.

In 1862 Walther reported an interesting case: A woman administered a large quantity of arsenic to another woman, and, observing that the action of the poison was slow, pushed her victim into the river, where she drowned. Postmortem examination, followed by chemical analysis, showed the presence of arsenic in the stomach, the spleen, and the liver, but none in the brain. The question arose on the trial as to whether death was due to the poison or to drowning. In order to solve this question Walther introduced into the stomach of each of 3 rabbits 2 grains of arsenic. Two of these animals were kept submerged in cold water for four and a half days, while the third one was allowed

to lie in the air. In the submerged animals no arsenic could be found in the liver or spleen, while arsenic was found in both of these organs in the third rabbit. Walther draws the following conclusions from these experiments: (1) Arsenic introduced into the living body is immediately absorbed, the process of absorption going on more or less rapidly according to conditions. (2) The absorption of arsenic stops immediately with death, but begins again with putrefaction, and its diffusion at that time is due to the formation of the arsenid of hydrogen. (3) When one finds arsenic in the liver or spleen of an undecomposed body it must be assumed that the poison reached these organs during life. (4) When arsenic is found diffused through the tissues of a decomposed body, it may have reached the various tissues either by absorption during life or as a result of putrefaction after death.

In 1882 the question of the postmortem imbibition of arsenic became the turning-point in a trial for murder in Michigan. The facts of the case, so far as expert testimony was concerned, are briefly as follows: Matthew Millard was accused of poisoning his wife with arsenic. The woman was taken sick on April 18, 1882. She was seen nearly every day, and sometimes twice a day, by a physician, and twice the attending physician had counsel. The woman had long been subject to uterine trouble; the nature of this trouble does not seem to have been understood by the attending physician. During her illness she vomited frequently, and, indeed, seldom retained either food or medicine. The testimony as to the symptoms manifested was so confused and conflicting that nothing definite could be made out of it. The attending physician thought that she had fever, but he never took her temperature. Death occurred on May 7th. After her death the husband requested the undertaker to embalm her body so as to preserve it until a casket could be brought from Detroit. The undertaker replied that he did not know how to embalm a body. The husband, who had once been an undertaker, requested the man in charge of the remains to obtain arsenic, saying that he (the husband) would embalm the body. On this point there was some conflict in the testimony of the undertaker and that of the husband. The undertaker swore that the husband had requested him to obtain strychnin, and he did so; while the husband swore that the request was for arsenic. The druggist did not keep any record of poisons sold, and consequently could give no definite testimony on the subject. The husband testified that he and his brother suspended a teaspoonful of white arsenic in a teacupful of water, and injected 1 syringe-ful into the mouth and 2 syringe-fuls into the rectum. The syringe that he claims to have used was an ordinary Davidson bulb syringe with rectal tube attached.

One hundred and five days after death the body was taken up and the stomach and rectum placed in one jar, and a piece of the liver and one kidney in another. The jars were sent to Professor A. B. Prescott for analysis of their contents. It might be remarked here that the husband stated, when the officers came to remove the body, that he had embalmed it with arsenic. Dr. Prescott found in the stomach and

rectum together about 20 grains of arsenious oxid, and from his analysis he calculated that the amount in the whole liver must have been from 6 to 15 grains, according to the size of that organ. Later, the body was again taken up, and the brain and a part of the muscles of the calf of one leg were sent to Professor Prescott for further analysis. In these Dr. Prescott failed to find any poison.

The question asked the experts on this trial, and the one on which the guilt or innocence of the accused seemed to hang, was in sum and substance as follows: Granted that white arsenic suspended in water was injected into the mouth and rectum a few hours after death, would it diffuse through the body to such an extent that it would be found in the liver and kidneys one hundred and five days after death?

One expert for the prosecution answered this question as follows: "If arsenic were injected into the stomach and rectum after death, it certainly would not reach the liver from the rectum, and I do not think it would reach the kidney. A small quantity of the arsenic might reach the portion of the liver in contact with the stomach. I do not think it would reach the kidney by diffusion after death. After death arsenic soon changes to an insoluble sulphid and ceases to diffuse. This would occur whether administered before or after death."

A second expert for the prosecution was very cautious in giving his opinion, as the following questions and answers will show:

"Q. If arsenic was put in the stomach after death, what, in your judgment, is the probability of its passing through into the liver by imbibition, or such portions of the liver as were not touched by the stomach?

"A. You must give me more factors than that to pass judgment on it. I must know whether the cavity of the abdomen was empty or whether it was full of fluid.

"Q. Suppose it was empty?

"A. I think if it was empty and the stomach was not lying upon the liver or touching the liver, there would be no imbibition to speak of.

"Q. Suppose it was not dry?

"A. It would pass. There would be imbibition from one organ to another, because chemists have demonstrated the fact that poisonous substances will pass through a bladder into the water on the opposite side. It is what we call dialysis."

Dr. Kedzie, for the defense, answered the question as follows: "I endeavored to find out whether arsenic would diffuse itself through dead matter in the same way that salt would. I tried to get the experiment in such a way that I could see the result. For this purpose I put a quantity of arsenic in a very dense solution of gelatin, which is an animal substance similar in properties to the tissues of the human body. This gelatin I put in the bottom of a large test-tube. I allowed this to cool so that it set into a solid mass. Then I took some more of the gelatin and put it into the tube, allowing it to cool and grow solid. In this last was put some hydrogen sulphid, so that if the arsenic should pass upward into the gelatin, it would be detected by the color. The

two portions of gelatin did not mix; they simply came in contact. After a moment there was a little tinge of color where the substances came in contact, and the yellow line gradually widened. At first it was only as thick as a piece of paper, then in twenty-four hours $\frac{1}{4}$ inch, the next day higher, and so on."

It might be remarked parenthetically at this point that this experiment formed a beautiful and practical illustration of the diffusion of arsenic.

The writer, testifying for the defense, answered the question as follows: "If arsenic should be injected into the rectum and stomach after death, I should expect to find it in the adjacent viscera within twenty-four hours. I believe this from my reading and from direct observation. Taylor reports a case where a stomach was wrapped in a piece of wall-paper which had been colored with arsenic. The side of the paper next to the stomach was that which was not colored. The next day the contents of the stomach were analyzed, and found to contain large quantities of arsenic which had passed from the paper through the walls of the stomach. A week ago last Thursday I took from the body of a person who had been dead but a short time parts of the intestines. I tied one end of a portion of the intestine so that a fluid would not pass through it save by diffusion. I then injected the intestine with arsenic suspended in water, tied the upper end, and suspended the piece of intestine in a dilute solution of hydrogen sulphid, so that as soon as the arsenic should pass through the walls of the intestine it would show by its color. When I first put it into the fluid there was no coloration, showing that there was no arsenic on the outside of the intestine. After three hours the fluid on the outside was colored, showing that the arsenic had passed through the walls of the intestine into the surrounding fluid. I also took another portion of the intestine and placed arsenic in the same manner inside, then suspended this in a dry beaker, and in about the same time I detected arsenic on the outside of the intestine. If within twenty-four hours after the death of Mrs. Millard arsenic to the amount of 1 teaspoonful had been injected into the stomach and rectum, and the body buried and examined one hundred and five days afterward, from my reading, and the experiments just given, I certainly would expect to find the arsenic in the liver from that injected."

The evidence from the books on the point of postmortem diffusion introduced in the trial well illustrates the wisdom of excluding statements from books in the giving of testimony in criminal cases. At that time Taylor's work on poisons was regarded as the great authority upon the subject, and statements from this book were introduced as testimony in the case. In the earlier editions of this work the experiments of Orfila and Kidd, which fitted the case in hand, are referred to, but the conclusions drawn by Taylor are not justified by the facts he gives. He says: "The effects of cadaveric imbibition have been greatly exaggerated. Observation shows that it is too limited in extent to affect materially the conclusion usually drawn from the detection of

poisons in the tissues. When a dead body is examined for a mineral poison, such as arsenic or antimony, shortly after death, and it is found in the liver or other soft organs, it is a fair inference that it was deposited in them during life."

It must be borne in mind that the use of arsenical embalming fluids was not so common in 1859, when Taylor wrote the above, as it was in 1882. But on another page he supposes that arsenic should be introduced into the stomach after death from natural causes, and concludes that even in such a case the expert would not be deceived, and could tell with certainty whether the poison was given during life or was introduced after death; a conclusion in which chemists of today cannot agree.

After the above-mentioned trial the writer concluded to investigate experimentally the question of the postmortem imbibition of arsenic. In this work he was aided by Dr. Dawson, then a student in the University of Michigan.

A large muskrat that had been caught by one of the students was killed and 3.24 grams of arsenious oxid suspended in cold water were injected with an ordinary bulb-syringe, with rectal tube attached, into the mouth and rectum. The rat was placed in a pine box and buried. After twenty-five days it was disinterred and the various organs removed and subjected to analysis, with the results shown in the following table:

Name of part examined.	Amount of arsenic, calculated as As_2O_3 , found.
Kidneys.....	0.00095 gram
Liver.....	0.01082 "
Lungs.....	0.19252 "
Stomach and contents.....	0.00686 "
Large intestine.....	0.40339 "
Small intestine.....	0.10157 "
Heart.....	0.02507 "
Brain.....	0.03960 "

Total As_2O_3 recovered, 0.78078 gram

It will be noticed that the lungs contained a much larger amount of arsenic than the stomach. Evidently the larger portion of that injected into the mouth passed down the trachea instead of going down the esophagus—indeed, the amount found in the liver is larger than that found in the stomach. It is likely that the poison passed from the lungs into the liver. The amount found in the brain is large, but in the muskrat the bones of the skull are thin in texture and not firmly united.

In a second experiment a cadaver was used. The person had been dead between two and three days when the injections were made. A teaspoonful of white arsenic was suspended in cold water and was injected by means of a common bulb-syringe with rectal tube into the mouth and rectum. The body was placed in a dry cellar, and allowed to remain there for twenty-five days. The various parts as given in the table below were then removed, weighed, and subjected to analysis. In dissecting the body it was observed that, although the cuticle had

decomposed to a certain extent, the internal organs were firm and remained in a fair state of preservation. This was true of all the parts removed except the brain, which was broken down to a semifluid condition.

The following table shows the part analyzed, its weight, the amount of arsenic estimated as arsenious oxid found, and the percentage of arsenic found in the various tissues:

Name of part taken.	Weight of part. Grams.	Weight of As_2O_3 .	Percentage of As_2O_3 .
Right kidney.....	104	distinct mirror	
Left kidney.....	90	0.00703	0.00782
Liver.....	865	0.08316	0.00961
Lower lobe of right lung.....	99	0.04333	0.04376
Heart.....	370	0.02199	0.00594
Transverse section of colon.....	85	0.02659	0.03128
Rectum.....	22	1.65000	7.50000
Spleen.....	48	0.00455	0.00947
Stomach.....	300	2.11200	0.70400
Brain.....	1028	0.00363	0.00035

It will be seen that while the right kidney contained only an unweighable quantity of arsenic, the left kidney furnished nearly as large a percentage as was found in the liver. I account for this by supposing that the liver caught up the greater portion of the arsenic passing down from the right lung, while on the left side the arsenic passed on into the kidney. Contrary to what was observed in the experiments on the muskrat, the stomach of the cadaver contained a large amount of arsenic, and it seems probable that some of the fluid thrown into the mouth passed directly into the stomach. I was somewhat surprised at finding arsenic in the brain, and the question arose, by what avenue did the poison reach this organ? It has been noticed that while throwing the fluid into the mouth at one time, when the bulb of the syringe was very forcibly compressed, a portion of the fluid returned through the nose. It is probable that some of the arsenic adhered to the roof of the pharynx and along the nasal passages, and from these penetrated the brain. However, arsenic placed in the stomach after death will diffuse in every direction and finally reach the brain.

Professor Kedzie, of the Michigan Agricultural College, at the same time, and wholly independently of the above work, made an experiment that he then reported to me as follows: "One of our students obtained a cat that had been killed a few hours before by a gunshot wound in the head. Under my direction a quantity of arsenious oxid suspended in water was injected into the stomach and rectum, and the cat was then buried for thirty-one days. At the expiration of this time the animal was taken up, the liver, spleen, heart, and kidneys removed without contact with the contents of the alimentary canal, washed with water, and then oxidized with potassium chlorate and pure hydrochloric acid. The residue was reduced with pure zinc and sulphuric acid, and the metallic arsenic collected in a glass tube. From two-thirds of the liver 22 milligrams of metallic arsenic were obtained, equivalent to 0.53 grain of arsenious oxid for the entire liver. The

heart, spleen, and kidneys were treated together, and from them I obtained 13 milligrams of metallic arsenic. There was thus obtained from this animal 35 milligrams of metallic arsenic, and if the whole of the liver had been used, there would have been 46 milligrams of metallic arsenic, equivalent to 0.89 grain of white arsenic obtained from viscera which could have received this arsenic only by postmortem diffusion from the contents of the alimentary canal. This result is directly opposed to the dictum of the older writers on medical jurisprudence, that imbibed arsenic in the viscera is proof of its administration before death."

Since one of the experts in the Millard case had given it as his opinion that arsenic would be converted in the alimentary canal into the sulphid, and that this would not diffuse, I made some experiments with this form of arsenic. The stomach of a dead cat was opened, and some moist sulphid of arsenic placed in this organ. The incision was carefully closed, and the animal buried. After sixty days it was taken up and arsenic was found abundantly present in the lungs, heart, liver, spleen, and kidney. The brain was not tested for the poison in this case.

The above-mentioned experiments have been confirmed by Miller, Witthaus, and others. In some of his experiments Miller provided against the direct absorption of arsenic from the pharynx into the brain. His statement is as follows: "The gullet was exposed by making an incision in the median line of the neck just below the larynx. Into the esophagus a longitudinal incision was made and a ligature placed immediately above the incision. Into the opening thus made a tube was passed through the gullet into the stomach. After the gullet was tightly secured to this tube the arsenical solution was poured down into this receptacle; the tube was then withdrawn, and the lower portion of the esophagus tied below the incision. Hence we are justified in claiming that all the poison recovered from any organ could not have reached that tissue in any other manner than by imbibition or a soaking process from the place of deposition—*i. e.*, the stomach. The spinal cord and brain were removed from every rabbit experimented upon before the thoracic or abdominal cavity was opened. The spinal cord was exposed in the usual manner by making two parallel incisions from the cervical to the lumbar region in the median line of the back, and the section thus mapped out removed by sawing through the laminae of the vertebrae. From a rabbit buried thirteen days the spinal cord, brain, contents of the urinary bladder, kidneys, and liver were removed. Owing to the special attention which we desired to give to the spinal cord, brain, and urine, these only were removed from a rabbit buried twenty-four days; also from a rabbit buried twenty-nine days the spinal cord and brain were taken. No urine was obtainable. These organs and secretions were placed in separate clean glass jars for chemical analysis." From the animals into which arsenic was thus introduced Miller obtained evidences of this substance in the brain, spinal cord, liver, kidneys, and urine.

He concludes his communication with the following: "On examining critically the preceding results we are doubtless justified in gleaning therefrom the following: That as the result of experimental research we have come in possession of indisputable evidence, demonstrated by strictly scientific methods, of the fact that when a poison is introduced into the stomach it can actually imbibe, soak, and diffuse itself into the various organs of the body, can be recovered from the liver, kidneys, spinal cord, brain, and interior of urinary bladder; also that the chemical evidence should not be held in the highest esteem and be given the place of first importance in all cases, as has hitherto generally been the case. It must be admitted that there are only very rare opportunities for the toxicologist to detect a discriminative method between ante- and post-mortem poisoning. But the microscopist, with his knowledge of the histologic and pathologic appearance of organs, may perhaps be able to discover, by rigid searching with his microscope, some prominent appreciable difference; for it is not improbable that there may take place certain specific changes in the histologic constituents of the organ due to the diffusion of a substance like arsenic, through the medium of the blood circulation during life, while these would not manifest themselves as the result of an after-death deposition."

Reese makes the following suggestions, which he thinks might be of benefit in determining whether a poison was administered before death or was introduced into the body after death:

"(1) A knowledge of the symptoms before death, where these are obtainable, will frequently throw much light on the case, although too much stress should not be placed upon symptoms merely, inasmuch as the symptoms of many diseases strongly resemble those of certain poisons. Thus, I have known several cases of fatal arsenical poisoning to have been mistaken for cholera morbus and treated as such by the attending physicians, and the certificate of death was made out, but in which I subsequently detected in the viscera large amounts of arsenic.

"(2) The chemical examination of the urine of the deceased. As is well known, the kidneys rapidly eliminate arsenic (and the same is true of other mineral poisons) from the body; and it is generally possible for the analyst to detect the poison in the urine both before and after death. Its discovery in this secretion may, I think, be regarded as very conclusive evidence of antemortem poisoning; for although it is true that the urinary bladder, in common with the other abdominal viscera, was found contaminated by the postmortem imbibition of the poisonous solutions in the experiments above detailed, yet I think it scarcely possible that the poison would percolate through the coats of the bladder so as to affect the contained urine. The record of the experiment was simply the production of the yellow substance on the surface of the organ. Nevertheless, in a capital case, where the evidence of poisoning hinged upon this particular aspect of the subject, I should not like to swear that such a thing might not be possible.

"(3) The finding of the poison on the exterior of the organs and not in their interior is, I think, very positive evidence of postmortem

imbibition, since in a true antemortem case the absorbed poison is always deposited in the interior of the organ quite as distinctly as on the outer surface. But practically this is often a difficult matter to decide, especially after the lapse of a long interval of time, and where the organs have become much broken down by decomposition.

“(4) The discovery of poison in the stomach after death cannot be regarded as absolute proof of its antemortem administration, since, as we have seen, it might have been injected after death; and there is also the further possibility that if introduced into the intestines through the rectum it might, by imbibition, penetrate into the interior of that organ, just as in the supposed case of the urinary bladder above alluded to.”

It will be seen from his own statements that no one of the suggestions made by Reese can be implicitly relied upon. Certainly no expert would be willing to give positive evidence from a most complete description of the most typical symptoms of arsenical poisoning. In other words, symptomatology alone is not sufficient proof of death from arsenic or any other poison.¹ The symptoms are suggestive, and cannot be regarded as anything more. The experiments of Miller have shown that arsenic may penetrate, when introduced after death, the bladder, and may be found in the urine. The finding of a larger amount of the poison in the periphery of an organ than in the interior is insufficient evidence to justify the expert in giving very strong testimony against the accused. The suggestion of Miller that pathologic changes may aid in determining whether in a given case the poison has been absorbed during life or has diffused after death, is of service only when the examination is made shortly after death, and it must be remembered that the perplexing cases are those in which the examination is not made until long after putrefaction has set in and the tissues are in such a condition that no histologist would be able to gain much positive knowledge from their study.

In 1889 Torsellini published some interesting experiments upon postmortem imbibition. He suspended dead frogs so that their hind legs were immersed in a solution of potassium ferrocyanid, and, after varying periods of time, he determined the extent to which this substance had diffused through the body, by treating various tissues with ferric chlorid. He found that after a few days the ferrocyanid had penetrated every part of the body. He also experimented upon warm-blooded animals. Some of his results may be condensed as follows: He introduced $\frac{1}{2}$ gram of arsenite of potassium dissolved in 200 grams of water into the stomach of a dead dog. The body was allowed to lie for seven days on its left side. At the expiration of this time chemical analysis showed the presence of arsenic in the brain, liver, lungs, and heart. In a second experiment he introduced 150 c.c. of a solution of arsenite of potassium into the stomach of a dead rabbit. This animal was placed on its right side. A chemical analysis made eighteen days later showed traces of arsenic in the brain, a large quantity in the liver,

¹ Compare p. 24 in section on General Principles of Toxicology.

lungs, and heart. In a third instance he placed a considerable quantity of the same solution in the large intestine of a rabbit. An examination eight days later showed no arsenic in the brain and cord, doubtful traces in the lungs, heart, and kidneys, but a very marked quantity in the liver. In still another experiment, after the introduction of the arsenic, the animal was suspended by its hind legs. After seventeen days arsenic in large amount was found in the liver and a smaller amount in the brain. In still another experiment the animal was suspended by its forelegs after the introduction of the arsenic. After eighteen days no arsenic was found in the brain and a small quantity in the liver. A large quantity of the arsenite of potassium was placed in the stomach of a dead dog. Forty-eight hours later a marked trace of arsenic was found in the brain, and large quantities in the liver, kidney, heart, and lungs. In one experiment the animal was not examined until one hundred and ninety-seven days after the introduction of the poison. The cranial cavity contained decomposed brain tissue in which arsenic was found in abundance.

Torsellini concludes from his experiments that arsenic introduced into the stomach after death may be found in the brain within from six to seven days, in the liver somewhat earlier, and in the lungs and heart earlier still. He also concludes that the position of the body after death determines the direction and rate of diffusion. When the analysis is not made until many months have passed, he decides that it is impossible to distinguish by chemical analysis between antemortem administration and postmortem diffusion.

In a case of trial for murder by the administration of arsenic Schaitter gave his evidence in favor of the belief of antemortem administration, notwithstanding the fact that only traces of arsenic were found in the liver, because the body that was exhumed five and one-half months after death was found to be distinctly mummified, and because vomiting and purging were symptoms observed during the last illness. While a discussion of the mummifying properties of arsenic does not come within the scope of this paper, it may be stated that mummification in and of itself is no positive proof of arsenical poisoning. Many mummified bodies contain no arsenic, while, on the other hand, many arsenical bodies rapidly decompose. Moreover, arsenic introduced into the body after death will act as a preservative almost, though probably not quite so powerfully, as that given during life.

The postmortem diffusion of certain corrosive poisons has been observed by numerous toxicologists. Strassmann has reported a case of this kind. A woman took a large dose of oxalic acid and immediately afterward hung herself. It was found on postmortem examination that the acid had penetrated without perforating the walls of the stomach, and had caused changes in the diaphragm, the left lung, the left wall of the heart, the spleen, the pancreas, and the suprarenal capsule. Similar observations have been made after carbolic acid poisoning.

The most recent experiments reported on the postmortem diffusion

of poisons are those of Strassmann and Kerstein.¹ These are interesting inasmuch as apparently they contradict some of those already mentioned. They suspended dead frogs so that their hind legs were immersed in a concentrated solution of gentian-violet. It was found that this coloring-matter very slowly penetrated the tissue, and after two days it had colored the skin and the underlying muscles, but not above the level of the fluid. When frogs were thus suspended in a 3 per cent. solution of potassium ferrocyanid, this substance penetrated the tissue more rapidly. In one experiment, after five days the ferrocyanid was found in the organs of the abdomen and thorax. In another instance, after four days, the whole animal was found to be permeated with ferrocyanid. Even the tongue gave evidence of the presence of this substance on being touched with a solution of ferric chlorid. However, the results obtained in these experiments were very variable, and at last they came to the conclusion that in those instances where the diffusion appeared to be so rapid the animal was not actually dead, and still carried on its lymph circulation. Some of their experiments with arsenic may be condensed as follows: One gram of pulverized white arsenic was placed in the stomach of a dead dog. The opening was closed, covered with collodion, and the animal allowed to lie for twenty-eight days. At the expiration of this time yellow spots were observed on the omentum and the small intestine. Upon microscopic examination these spots were found to consist of bacteria and certain crystals without definite form. A chemical examination of the spots showed the presence of arsenic. In a second experiment 5 grams of pulverized white arsenic were suspended in 80 c.c. of water and then introduced into the stomach. Twenty-one days later an examination was made. The kidneys, the spleen, and the brain were found to be free from arsenic. The left half of the liver contained a large amount of arsenic, while the right half contained arsenic in much smaller quantity. The lungs contained a large amount of poison. In still another experiment 50 c.c. of a 1 per cent. solution of the arsenite of potassium was introduced into the stomach. Thirty days later an analysis showed the brain and both kidneys free from arsenic, while the liver contained a large amount. The conclusions which they draw from their experiments may be stated as follows: (1) Different substances, such as arsenic, diffuse through the dead body. This diffusion goes on slowly and extends from one organ to that immediately adjacent, and from this on to the next. (2) In consequence of this diffusion such substances as arsenic may after some days diffuse from the stomach into the adjacent organs. (3) If the left kidney contains arsenic while the right contains none, it may be inferred that the poison is diffused from the stomach after death. If both kidneys contain arsenic during the first week after death, its administration during life may be assumed. (4) A separate examination

¹ In the report of experiments made by these investigators (*Virchow's Arch.*, vol. cxxxvi) a résumé of the literature of this subject is attempted, but it is quite evident that they did not consult the original articles. They have taken Taylor's interpretation of Kidd's experiments, have attributed Vaughan's experiments to Prescott, and have made it appear that the last-mentioned chemist is a Frenchman.

of the left and right lung, also of the left and right portions of the liver, may aid in determining whether the poison has been introduced during life or after death. (5) Arsenic does not diffuse from the stomach into the brain within four weeks. From the pharynx it may pass into the brain in a shorter time. (6) If the poison has been introduced into a part of the dead body other than the stomach, an examination of the place of introduction and of tissues more or less distant should be made.

While most of the experiments on the postmortem imbibition of poisons have been made with arsenic, it must not be inferred that this substance diffuses through the body more readily than other poisons. All crystalline substances will diffuse through animal tissue.

For some years before and for a few years after the publication of the first edition of this work (1904) arsenical embalming fluids were largely used throughout the United States. Gradually these fluids were discontinued, partly by legal enactment and partly by the demonstration to undertakers that formaldehyd solutions are much superior in embalming and at the same time eliminate the possibility of leading to complications in medicolegal investigations. So far as I know, formaldehyd solutions are now used almost exclusively for embalming purposes, but this does not do away with the desirability and even the necessity for the toxicologist to be thoroughly posted on the postmortem imbibition of poisons.

The following illustrative cases in my toxicologic practice since 1904 are examples: In an Iowa case, occurring while arsenical embalming fluids were still in use, there were presented certain important facts. A man was accused of having poisoned his wife by the administration of arsenic. Her body was embalmed with an arsenical fluid. Some weeks after death it was exhumed and chemical examination showed arsenic abundantly and widely distributed throughout the tissues. There was, however, a typical arsenical ulcer in the stomach, and this part of the tissue was turned over to a committee of distinguished pathologists who decided, from their histologic studies, that the ulcer was produced during life and could not have been due to the embalming fluid. The testimony of the pathologists was so positive and convincing that the accused was convicted. Since that time I have in all instances insisted that there should be a histologic examination of every case of suspected arsenical poisoning brought to me for chemical study. In my opinion, this is a wise precaution not only in cases in which there is the possibility of postmortem imbibition, but in cases in which the amount of arsenic recovered is small. It is not within the province of this article to go into the characteristic microscopic lesions induced by arsenic, mercuric chlorid, or any other chemical poison.

In a Michigan case an elderly couple were living alone in a detached house in a village. Both were childish, petulant, and quarrelsome. It was well known to the neighbors that frequent wordy altercations were indulged in between man and wife. She slept on the second floor, while he occupied a room below. One morning about seven o'clock the husband went upstairs and found his wife dead in

bed. There could be no testimony concerning symptoms, because she was in her usual state of health when she retired. There had been no vomiting. By 10 o'clock on the same morning her body had been embalmed. By two o'clock in the afternoon a postmortem examination had been made and the stomach and liver removed, and these were subsequently sent, with a specimen of the embalming fluid supposed to have been used, to a competent chemist. The chemist found 68 grains of arsenic in the liver and only a fraction of a grain in the stomach. There was no question as to the competency of the chemist or the accuracy of the results. I was consulted by both the prosecuting attorney and the lawyer for the defense. I held that the relative amounts of arsenic found in the stomach and in the liver were not consistent with the supposition that the poison was administered during life and that the embalming fluid did contain arsenic, notwithstanding the positive statement of the undertaker, whose honesty was not in question. Finally, I induced the prosecuting attorney to investigate the embalming fluids kept in stock by the undertaker, and this resulted in showing that a bottle containing an arsenical embalming fluid stood among other bottles on his shelves and that the marks on the shelf and the condition of the stopper showed that the bottle had been recently removed and replaced. The undertaker himself was convinced from this demonstration that he had not used in this case the fluid which he had submitted to the chemist, but had employed the old arsenical fluid. On this evidence the prosecuting attorney dropped the case.

In a case in Connecticut both the chemists for the prosecution and for the defense found large quantities of arsenic in the stomach, liver, and other organs. The experts for the prosecution demonstrated to the court the presence of crystals of arsenous oxid in the contents of the stomach. There was no arsenic in the embalming fluid which, according to the testimony of the undertaker, was used. The chemists for the defense claimed that, notwithstanding they found no arsenic in the embalming fluid, this was a case analogous to the one just mentioned above, and that the large amount of arsenic found in both stomach and liver could have been due only to the employment of an arsenical embalming fluid. When asked, however, to explain how the arsenite of potassium or sodium, which the embalming fluid must have contained, if it contained any arsenic, could be converted into crystals of arsenous acid in the stomach, they failed to satisfy the court and the jury and conviction resulted, and was subsequently justified by confession.

THE DESTRUCTION AND ATTEMPTED DESTRUCTION OF THE HUMAN BODY BY FIRE AND CHEMICALS

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THE destruction of the human body, more or less complete, usually with the purpose of removing evidence of a previous crime, is a somewhat common occurrence in criminal cases and raises a number of important questions for the medical jurist and expert. Fire is the agency usually resorted to and deserves chief consideration, chemicals having been used to only a very limited extent.

DESTRUCTION BY FIRE

The questions arising in consequence of the attempted destruction by fire may be considered under four heads: (1) Where all material sources of evidence have been removed; (2) where there remain ashes from which evidence as to the former existence of an animal body can be derived, but the human character cannot be distinguished; (3) where the remains permit the recognition of their human origin; and (4) where the personal identity of the body can be determined with more or less probability.

In connection with each of these numerous matters of inquiry may arise, such as the time and fuel required for the more or less perfect destruction of the body, the differentiation of the effects of fire applied before and after death, the effects of fire in producing fractures of bones, etc.

Complete Destruction of the Body by Fire.—When the human body has been completely consumed by fire and the ashes have been disposed of, the material evidences of the crime are obliterated. The medical witness may, however, be called upon to answer certain questions as to the possibility of the destruction of the body, the time required, the amount and quality of fuel needed, as well as to give his opinion in regard to the meaning of odors, etc., which may have been perceived by others at the time of the alleged destruction.

Time and Amount of Fuel Required.—One of the most important questions relates to the time required to burn a body and the amount of fuel necessary for the purpose. An exact answer to these questions can be given only as the result of actual experiments, conducted under conditions resembling as nearly as possible those under which the

alleged burning took place, but an opinion can be formed as to the approximate time required from observations already made. At the trial of Professor Webster in 1850,¹ Dr. Woodbridge Strong testified that he undertook to burn a body in the open air, but after working all night there was still much unconsumed. The kind of fuel is not stated, but was probably wood. In the Calder case² it was in evidence that the two murdered men were placed on a great fire of logs at 2 P. M.; the fire was replenished from time to time, and at midnight the bodies had been mostly consumed; at daybreak only ashes and cinders were left, among which subsequently several teeth and many parts of charred bones were found.

As the result of experiments in connection with the trial of Roxalana Druse in 1885³ Dr. A. Walter Suiter found that a human body weighing 140 pounds could be burned in a wood-stove in eight hours, and that only $1\frac{1}{2}$ pounds of fuel such as was used in this case (dry pine shingles) would be required for each pound of mixed animal tissues. It was found that the tissues first lost water and then the dry mass burned readily.

In the celebrated Pel case in Paris in 1884⁴ Brouardel performed experiments with a small kitchen stove such as Pel used. He found that a body could be consumed at the rate of $1\frac{1}{2}$ kilograms, or $3\frac{3}{4}$ pounds, per hour, so that a corpse weighing 60 kilograms, or 132 pounds, could⁵ be consumed in forty hours, using charcoal as fuel. The weight of ashes left in this case was 6 kilograms, or 13 pounds.

No very marked odor is necessarily occasioned by the burning of the body. The first part of the process in which the flesh is deprived of water and begins to char is usually accompanied by an odor resembling that of meat scorched in cooking, but the further burning does not of necessity give off much odorous gas. A great deal depends, however, on the method of combustion—the more nearly perfect and rapid it is the less the odor, while in the case of slow and imperfect combustion the odor may be quite offensive.

According to experiments conducted by Professor L. Hektoen,⁵ in burning three bodies in a furnace upon a bed of glowing anthracite coal, the body can be consumed in a very short time. The fire-box of the furnace in this case was 4 feet long, 35 inches wide, and 18 inches high. In each experiment a body was destroyed in less than an hour, so that nothing was left in its original form except the bones of the pelvis. The extremities were removed in each case and placed by the side of the body in the furnace.

When alcohol, petroleum, or oil is used as fuel, the time necessary for combustion, according to Descoust, Robert, and Ogier,⁶ must be at least an entire day.

¹ Boston Medical and Surgical Journal, 1850, xlii, pp. 166, 167.

² 59 Pacif. Ref., 903.

³ Transactions Medical Society of State of New York, 1887, pp. 417-428.

⁴ Annales d'Hygiène, Paris, 1886, 3 S., xv, pp. 113-123.

⁵ Personal communication.

⁶ Annales d'Hygiène, Paris, 1894, 3 S., xxxi, p. 533.

In connection with a murder trial held in Appleton, Wis., in 1906, Dr. John F. Golden,¹ of Chicago, conducted an experiment to determine how quickly the human body could be consumed by a fire in the open air. A bonfire was started, green maple wood being used for the purpose. The body of an adult man weighing about 160 pounds and about 5 feet, 8 inches in height was placed on the fire, and from time to time additional wood was added so as to keep up a continuous burning. The body was consumed in four and a half hours, two-thirds of a cord of 16-inch green-maple wood having been used. During the process no disagreeable or peculiar odors were evolved. In the resulting ashes fragments of bone were found, the largest not over 2 inches in length, and some of these, although small, were identified as human by Dr. George A. Dorsey, at that time of the Field Columbian Museum of Chicago. The pieces of bone recovered were sufficient to fill a large cigar box.

Determination of the Animal Source of the Ashes.—When the ashes are left in the stove or can be obtained and identified, they may furnish positive evidence of the consumption of an animal substance. If the combustion has not been complete the ash will have a brownish color, which indicates the probability of an animal origin. In some cases of incomplete combustion the ashes become permeated with a substance of a fatty consistence resembling tallow, which may be a melted or saponified animal fat. The ashes should be examined for these appearances, and such parts be reserved for careful chemical analysis as may be able to reveal the source of the fat. The principal evidence of the animal origin of ashes is found in the presence of a large amount of phosphates, especially the phosphate of calcium derived from the burning of bones. The following table gives the composition of the ash of the bones of various animals²:

	Human.	Ox.	Turtle.	Guinea-pig.
Calcium phosphate.....	83.89	86.09	85.98	87.38
Magnesium phosphate.....	1.04	1.02	1.36	1.05
Calcium in other combination.....	7.65	7.36	6.32	
Carbon dioxid.....	5.73	6.20	5.27	
Chlorin.....	1.80	2.00		
Fluorin.....	2.30	3.00	2.00	

The ash of muscle contains somewhat more than one-third its weight of phosphoric anhydrid, which is mostly combined with potassium instead of calcium.³ The ash of human bones constitutes from 60 to 70 per cent. of their weight.⁴ From these facts it may be possible to calculate from the amount of phosphates found in the ashes the amount of bone consumed. This was done in the Druse case, with the result that the weighed fragments of bone and the computed weight of bone represented by the calcium phosphate found in the ashes were equivalent to about two-thirds of the weight of a human skeleton. No fragments

¹ Personal communication.

² Zalefsky, quoted in Simon's *Physiological Chemistry*, p. 387.

³ Gautier, *Chimie applique à la physiologie, à la pathologie et à l'hygiène*, vol. i, p. 308.

⁴ Gautier, *op. cit.*, vol. i, p. 352.

of bones of the trunk were found, so that it is probable that the bone ashes were deposited in part in another place. The ashes of ordinary wood have a very different composition, containing from 10 to 30 per cent. of compounds of potassium, chiefly carbonate, and phosphates corresponding to only from 4 to 7 per cent. of phosphoric anhydrid,¹ Coal-ashes consist chiefly of silica, alumina, lime, and oxid of iron. They contain but little potassium compounds and from 0.4 to 1.2 per cent. of phosphates, calculated as phosphoric anhydrid.²

Identification of the Human Character of the Remains.—

Unless the combustion has been very complete, fragments of bone are likely to be left and these may furnish evidence, more or less conclusive, that the body consumed was that of a human being. It is not possible within the limits of this article to establish the identity of the human skeleton, but it may be well to indicate a general method of procedure by which this evidence may be made most available. After picking out from the ashes any large fragments of bone, the ashes should be sifted through a series of sieves and the fragments obtained carefully sorted and diligently studied. Fragments which cannot be recognized should be compared with other fragments in order to find any which fit each other so as to show that they are fragments of the same bone. These should be attached to each other for subsequent study. The identification of such fragments as parts of the human skeleton requires a thorough knowledge of comparative as well as human anatomy. The animals whose remains are most likely to be present in such ashes are the domestic animals, but a skilful defense is likely to exhaust every resource to throw doubt on the human origin of the fragments. The bones likely to leave fragments characteristic of the human skeleton are those of the skull and of the feet and hands. The temporal bone seems very likely to be left, and is a strong evidence of human origin. In the Luetgert case (see below) a temporal bone (greatly softened but still recognizable), found near the furnace, seemed to have passed through both the boiling alkaline bath and the furnace fire. The teeth are especially important, and are, moreover, quite resistant to the action of fire.

Determination of Age, Sex, and Personal Identity.—If the body has been but partially consumed, questions as to age, sex, and personal identity and the origin of bruises and fractures may be raised. The changes in the shape of the lower jaw in consequence of the loss of teeth are the principal means of identification of the age of the deceased. The discovery of hairs may also furnish evidence. Distinction of sex may be possible by the characters of the male and female pelvis. The size and shape of the bones, and the prominence of the muscular ridges may permit an inference as to the size of the individual and the development of the muscular system.³

¹ Meyer's *Konversations-Lexikon*, vol. i, p. 979; Richardson and Watts' *Chemical Technology*, i, p. 440.

² Meyer, *op. cit.*, vol. i, p. 979; Watts' *Dict. Chem.*, vol. i, p. 1031.

³ For a discussion of the data concerning the age, size, and sex derived from the skeleton, see Dwight, *Medical Communications*, Massachusetts Medical Society, 1878, 2 S., viii, p. 169.

The *personal identity* of the victim is an important question upon which the examination of remains mutilated by fire is not likely to throw much light. In the Webster case identification was attempted by measurement of the parts of the body which had not been consumed, but the most that witnesses could establish was that these measurements were not inconsistent with the size and muscular development of Dr. Parkman, whose body was missing. The examination of artificial teeth furnished more important evidence, although this evidence was questioned by some dentists. It was generally agreed, however, that a dentist would be able to recognize his own work.

Were the Burns Produced Before or After Death?—Where the injury to the body has been slight, the question may be raised whether the appearances are due to burns received before or after death. The distinctive characters of a burn received before death are the characteristic vesicles, the area of inflammatory redness around the burned spot, and the presence of pus or granulation tissue underneath the dead skin.

Experiments undertaken by Christison, Taylor, and Casper indicate that vesication is a sure sign of burns produced before death, except perhaps in the case of anasarctous bodies, but lack of blisters is not a sure indication that the burning was not done before death. The experiments of Gräff,¹ of Maschka,² and of Taylor³ show, however, that the effects of heat upon the living and the *recently* dead are very similar. The blisters raised upon the dead, except in the case of dropsical subjects, contain air instead of serum. The serum exuded after death is said not to be coagulable by heat and nitric acid, while that in blisters produced before death is coagulable by these reagents.

The line of redness that forms around a burned part is due to a vital action and is never seen in case of burns produced after death. The absence of this appearance is not certain proof that the burn was received after death, but its presence may be regarded as positive evidence that the burning took place while the person was living. Similarly, the discovery of pus or granulation tissue is positive evidence of a vital action, and hence of the occurrence before death.

Were the Wounds Observed Produced Before Death, or are they the Effect of Heat?—The action of heat upon the body may produce the appearance of wounds. Apparent wounds of the soft parts are produced by the giving way of tissues weakened by the heat in consequence of stress of some kind. These tears are apt to be more ragged than wounds made before death, the fissures extending in several directions.

Fractures of bones occasioned by heat may be mistaken for fractures which occurred before death. In fractures occasioned by heat more superficial cracks are observed and the fracture seems never to extend beyond the portion of bone whose structure has been injured by the heat.

¹ Prag. Vierteljahrsschr., 1850, iv.

² Canstatt's Jahresbericht für 1852, vii, p. 46.

³ Medical Jurisprudence, 5th edition, 1855.

Tardieu,¹ after a conflagration in Paris in which a number of persons perished, made the following observations, according to Wharton and Stillé:² "The bones were dried and brittle, and in the long bones fractures with obliquely splintered and charred ends were observed, differing distinctly from the character of ordinary fractures. In the flat bones, which were thinned by heat, the fractures caused by the heat assumed the form of fissures confined to one surface, and not penetrating the substance of the bone. The intervertebral disks were contracted in their diameters. Teeth and cartilage seemed to resist the action of fire more than other hard parts. Some of the viscera were mummified. The blood of the heart, aorta, and other large vessels presented an extraordinary appearance, resembling wax or fatty matter, of a most beautiful carmin color."

Casper³ cites the case of five carbonized individuals, a man, a woman, and three children, who presented the following appearances:

"The general appearance alone denoted them to be human. Their respective pelvis also permitted the distinguishing with probability which was man and which woman. All the five were thoroughly carbonized and black, all their cavities laid open, and not a trace of soft parts any longer visible. From almost every skeleton single parts—an arm, a hand, a foot, or a whole extremity—were broken off and wanting."

The following cases of more or less completed destruction of the body by fire for criminal purposes illustrate many of the preceding points:

CASE 1.⁴—On November 23, 1849, Dr. George Parkman disappeared, having been last seen in the neighborhood of Harvard Medical College, Boston. Attention of people living near the college was drawn to unpleasant odors as of burning flesh issuing from the college. Search of the laboratory of Professor John W. Webster resulted in the discovery of parts of a body consisting of a thorax, a pelvis, two thighs, and a left leg. The parts of the spinal column of the thorax and pelvis fitted exactly and the left leg fitted the left thigh. The flesh showed indications of having been subjected to the action of a strong solution of caustic potash. From the ashes of the assay furnace a large number of fragments of bone were recovered, comprising fragments of the cranium, thirty to forty pieces, a fragment of the temporal bone, the coronoid portion of the lower jaw, probably of an elderly person, another part of the lower jaw, a fragment of the atlas, the body of a cervical vertebra, a fragment of the humerus, the terminal phalanx of a finger, a fragment of the tibia, a fragment of a metatarsal bone, the right os calcis, the right astragalus and several pieces of artificial teeth. There were also many unidentified fragments and a fragment of the ulna and the olecranon process. A considerable portion of a plate for artificial teeth, as well as a considerable amount of gold, were found in the ashes. Dentists testified as to the identity of the plate of artificial teeth, comparing it with the models from which they had made teeth for Dr. Parkman. The medical witnesses testified that the measurements of the body and the muscular development were not inconsistent with what they knew of Dr. Parkman. For the defense, dentists testified that the plate of teeth would fit many mouths and that they did not believe identification possible. In rebuttal the prosecution brought evidence that a dentist would be able to identify his own work. The accused was convicted and afterward made a full confession.

CASE 2.⁵—In 1861, in North Carolina, a man was indicted for the murder of Peggy Hilton *alias* Peggy Isly. She disappeared December 1, 1859, and ten days

¹ Annales d'Hygiène, Paris, April, 1854.

² Wharton and Stillé, Medical Jurisprudence, 3d ed., vol. ii, part 2, p. 762.

³ Vol. i, p. 308, London translation, 1861.

⁴ Boston Medical and Surgical Journal, 1850.

⁵ State *vs.* Williams, 7 Jones' Law, North Carolina, 446.

later a log heap was discovered on the defendant's land, still burning. Search of the ashes resulted in the discovery of many fragments of bone and a substance resembling tallow. A creek near by was dragged, and bones, hair-pins, a button, an eye of a hook and eye, etc., were found. Four physicians and one dentist were examined and stated that they recognized among the bones part of a human skull and part of the cheek-bone of a human being. The dentist deposed to the identity of human teeth among the bones exhibited in court. Upon appeal to the Supreme Court this evidence was held to be valid.

CASE 3.¹—December 18, 1884, William Druse was killed by his wife, Roxalana Druse, and the body burned in a wood-stove with the aid of dry pine shingles as fuel. The ashes were deposited under a clump of bushes about half a mile from the house, and consisted of a chaotic mass of finely pulverized wood- and bone-ash, bits of charcoal, and small fragments of bone, of irregular form, which could not be recognized as parts of the human skeleton without careful and diligent study. By careful sifting of the ashes numerous fragments of bone were discovered. Among them were six fragments recognizable as parts of a human cranium, twenty-three fragments probably of a human cranium, part of an alveolar process, the fang, neck, and crown of a lateral incisor tooth, thirteen fragments of fangs of teeth, the head of a human radius, fragments of patellæ, ten fragments of the hand and foot, three fragments of human cranium, one showing characteristic suture, two fragments of cervical vertebrae, and four fragments of a human temporal bone. No bones of the trunk were found, and subsequent testimony showed that this part had been deposited elsewhere. Conviction was secured.

CASE 4.²—In Paris, in 1884, a man named Pel was accused of the murder of his mistress, Elise Bohmer, by poison, and of subsequently destroying the body by fire. The woman was taken sick July 2d, and after the 12th was seen no more. It is supposed that she died on that date. Odors suggesting a corpse in the apartments of Pel were noticed by several neighbors. Notwithstanding the unusually hot weather it was observed that he kept up a fire in his kitchen stove, and the light from flames in the stove shone through the windows until he hung a curtain to intercept it. After some days the neighbors, being suspicious, put up a ladder and obtained a view of his premises. Suspicion having been aroused, the premises were searched and various articles seized for examination. Among them were a number of drugs and the contents of the stove, as well as the stove itself. Upon the handle of a saw some spots were discovered which proved to be blood. An examination of the ashes showed them to be wood-ashes, and no fragments of bone could be discovered in them. It is probable that the ashes produced by the burning of the body had been disposed of before the stove was seized. This case is one in which the evidence of the destruction of the body and the previous poisoning was purely circumstantial. The medical expert, Brouardel, was able to say that the symptoms from which the woman suffered during her sickness resembled arsenic poisoning, but might have been due to other mineral poisons. He was also of the opinion that the odors observed indicated the presence of a cadaver in the rooms between the 12th and 17th of July. The flames seen and the fire at unusual hours despite the very hot weather were evidences of the burning of such a body. The time was ample, as only forty hours were required, while Pel had one hundred in which to dispose of the remains. Pel was convicted. (It is evident that a conviction in such cases should rest upon very conclusive circumstantial evidence, and the province of the medical expert, at least in this country, should be limited to stating the results of scientific observation and experiment upon the various conditions under which the body can be destroyed by fire.)

CASE 5.³—In the case of Durant, accused of murdering and attempting to destroy by fire his wife, daughter, and a man named Devaux, the question arose whether the greasy material saturating the clothes of the victims was human fat coming from the cadavers or oil with which they had been saturated in order to burn them more readily. The expert decided that the material was animal fat, probably human.

The following additional cases may be consulted:

Leuret, corpse of a woman whose head was burned, blood coagulated between the cerebral convolutions; suspicion of homicide; contradictory reports; conviction.⁴

¹ Transactions of the New York State Medical Society, 1887.

² Annales d'Hygiène, Paris, 1886, 3 S., xv, pp. 113-123.

³ Ibid., Paris, 1894, 3 S., xxxi, p. 533.

⁴ Ibid., Paris, 1835, xiv, p. 370.

Case of Regina *vs.* Jarvis, New South Wales Medical Gazette, Sydney, 1873-74, iv, 80-89.

Girdwood, Canada Medical and Surgical Journal, 1874.

Chemische Untersuchung einer Asche, Sammt. gericht. arztl. Gutacht. d. Prag. med. Fak., 1867. 3 F., 346-348.

In the Landru case, tried at Versailles, France, in November, 1921, it was claimed by the prosecution that the prisoner had killed eleven women whose bodies were found burned. The pieces of bones discovered in the ashes came from animals the prisoner claimed, but fragments of these bones were identified by experts for the State as being of human origin, even though they were small and had been through fire. The accused was convicted.¹

Strassmann, Ueber eine Erscheinung bei Verbrennung, Preuss. med. Beamte. Veroff., Berlin, 1898, xv, 103-110.

State *vs.* Ah Chuey, 14 Nevada, 79; Regina *vs.* Murphy, 4 Wyatt, Webb, and A'Beckett, 63 (Victoria, 1867); People *vs.* Alviso, 55 Calif., 230 et seq., 1880; Gay *vs.* State, 49 S. W. Rep., 612-617 (Texas, 1897); Kugadt *vs.* The State, Texas Criminal Reports, vol. 38, p. 681 (Texas, 1898); State *vs.* Calder, 59 Pacif. Rep., 903 (Montana, 1900).

CREMATION

In the destruction of the human body by cremation the corpse in a wooden coffin, from which the metallic handles and name plate have been removed, is placed in an apparatus especially devised for the purpose, called a retort, and heat, produced either by the combustion of ordinary illuminating gas or petroleum, is applied. The temperature used is about 3200° F. (or 1760° C.). A body of ordinary size is completely cremated when gas is used as a fuel in one hour; when petroleum is used, from one and a half to two hours are required. The ash which remains, which consists entirely of mineral substances, all organic compounds having been destroyed, weighs from 5 to 9 pounds, depending on the size of the body. Immediately after the cremation the skeleton of the body is left intact in form, its abundant mineral constituents preserving the contour. It is, however, easily crushed and reduced to a powder, and it is then mixed with the remains of the rest of the body. The screws and nails from the wooden casket are removed from the ash by a magnet.

Artificial porcelain teeth are but little affected by the process and may be found in the ashes, but the natural teeth are destroyed. Gold fillings in the artificial teeth are melted and disappear.

Cremation, therefore, proves a bar to almost all medicolegal examinations. The weight of the ashes may afford some suggestion as to the size of the individual, and if artificial teeth are discovered in the ashes they may perhaps be identified by the dentist who introduced them. Very little else can be determined.²

Whatever may be the advantage of cremation for hygienic or sentimental reasons, from a medicolegal standpoint it is wholly objectionable.³

¹ For the details of this remarkable case, consult the daily French journals of that period, such as *Le Temps*, beginning November 9, 1921.

² Compare General Principles of Toxicology, vol. ii, p. 65.

³ For further information concerning the subject, consult Knopf, *Cremation Versus Burial*, Am. Jour. Pub. Health, 1922, 12, p. 389.

DESTRUCTION BY CHEMICALS

Destruction of the body by chemicals is rare in the annals of crime. The reasons for this are obvious. The laity is not, as a rule, acquainted with the action of chemical agents on animal tissues, nor are the necessary corrosive chemicals and suitable vessels in which to use them usually obtainable with sufficient readiness for this use. It is not surprising, therefore, that only a very small number of cases are known in which criminals have resorted to chemical agencies for the purpose of destroying the body to remove evidence of a previous crime.

Although the number of chemicals that might be used for the destruction of the body is considerable, there are two classes only that are of material importance, namely: the strong acids and the corrosive alkalis. Of the former, nitric, sulphuric, and hydrochloric acids are the most rapid and pronounced in their action, and it is quite possible by either of these to effect the complete disintegration and destruction of a human body if a sufficient amount of the chemical is used, especially if heat is employed.

Nitric acid is particularly efficient in its destructive action on animal tissues, attacking, disintegrating, and liquefying practically every portion of a body, the skeleton included. During its action lower oxids of nitrogen are given off in greater or smaller amount according to the heat applied, and the resulting solution is of a yellow or brownish-yellow color. Sulphuric acid¹ is also highly destructive of animal tissues as of most other organic bodies, but it is rather less potent than nitric acid in securing complete and rapid disintegration and liquefaction. The solution obtained is of a dark-brown or black color, and if the heat used is considerable, carbonization of the material ensues, attended with the evolution of sulphur dioxid. Hydrochloric acid is somewhat less active in corroding the body than either nitric or sulphuric acid. No gas is given off from its action on the tissues, and the resulting liquid is usually of a dark-bluish or purple color. Of either of these acids as ordinarily found in commerce a weight about equal to that of the body acted on is required for complete disintegration. A mixture of nitric with sulphuric or hydrochloric acid is more active than either acid alone, and hydrochloric acid becomes much more energetic in its effect on organic tissues if used in conjunction with potassium chlorate. These acids, and especially the mixtures named, are largely used in toxicology to destroy the different organs of the body in searching for mineral poisons.²

Strong alkalis, such as potassium and sodium hydroxid, particularly when aided by heat, are rapidly destructive of all parts of the body except the bones; these are only slowly acted upon and at the most are but imperfectly disintegrated, although rendered brittle and easily friable. A knowledge of the destructive action of strong alkalis on the

¹ Consult *Note medico-legale sur la possibilité de faire totalement disparaître un cadavre au moyen de l'acide sulfurique ordinaire*, Comptes rend. de la Société de Biologie, Paris, 1883, 7 S., v, 5.

² Compare *General Principles of Toxicology*, vol. ii, p. 43.

body is rather more general among the people than information as to the effects of acids. Alkalis, moreover, are usually more easily obtained without exciting suspicion than are acids, the former being so extensively used by the people in making soap, in washing, and in many other every-day operations; and, finally, hot alkaline solutions are far less destructive than acids to metallic and wooden vessels, and consequently can be much more readily used in acting upon a body than acids. For these reasons the destruction of the human body has been attempted more frequently by strong alkalis than by the corrosive acids.

Perhaps the best known case in which chemicals have been used for the destruction of the body is the Luetgert case, tried in Chicago in the autumn of 1897. The case illustrates most of the important points in connection with the subject. Louisa Luetgert, wife of Adolph L. Luetgert, a prosperous sausage manufacturer of Chicago, disappeared from her home, adjoining the sausage factory, the evening of May 1, 1897, and was last seen going into the factory with her husband. As the woman did not make her appearance again, neighbors and relatives in a few days became alarmed and reported the disappearance to the police. Upon searching the sausage factory they found in the basement a large wooden tank supplied with steam-pipes, in the bottom of which there still remained, although the stopper for emptying it had been removed, a quantity of a reddish-brown, strongly alkaline fluid mixed with a large number of small flakes and a few larger fragments of bones. Upon careful search there were also found at the bottom of the tank a gold ring bearing the initials "L. L.," which was identified as Mrs. Luetgert's wedding-ring, and a plain gold guard-ring worn by Mrs. Luetgert to prevent the wedding-ring from slipping from the finger. A part of an artificial tooth corresponding to one which Mrs. Luetgert was known to have worn was picked up from the floor by the side of the tank. Luetgert, the husband, was arrested and tried for the murder of his wife. The theory of the state was that he had killed her either by choking or by stabbing with a knife, and then, to remove the evidence of his crime, had placed her in the tank in the basement, had covered the body with a solution of caustic potash, and by means of the steam-pipe connected with the vat had heated the solution until the remains had been disintegrated and the soft parts dissolved. It was a matter of record that he had bought a considerable quantity of crude potash but a short time before, and it was in evidence that he had caused it to be dissolved in the tank in question. From the weight of the potash bought and from the size of the tank it was calculated that the solution contained from 5 to 8 per cent. of potassium hydroxid. The bones, which had escaped destruction in the vat, together with the woman's clothing, were then, it was alleged by the state, placed in the fire under the boiler and consumed. In support of this position many witnesses were called and testified to numerous quarrels between husband and wife; to her going to the factory the night of her disappearance; to his being seen later in the night intently watching some process that was going on in the tank in the basement; to his building up a considerable

fire under the boilers the following morning, although the factory had been shut down for repairs; and to numerous other suspicious circumstances. The most important evidence, however, for our present purpose was the scientific testimony given: Ashes, believed to have been those removed from under the boiler the day after the crime, were found upon analysis by the writer to contain several times the amount of phosphate normal to the fuel used; but this fact did not carry great weight, as it was shown that it was customary to throw into the boiler fire the sweepings of the factory, including many small bones. Among the fragments of bone found in the vat were a few (a sesamoid, the posterior tip of a rib, the end of the third metacarpal, and the second

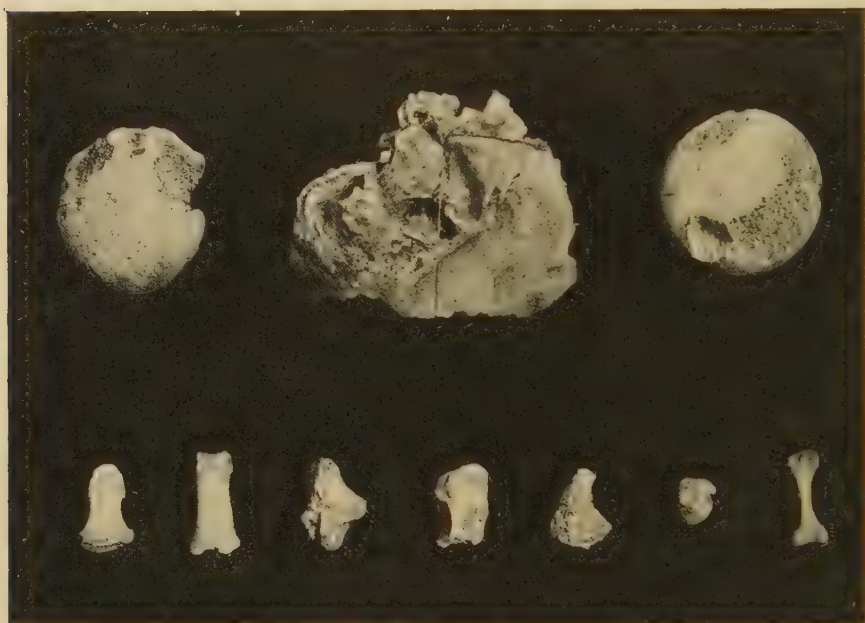


FIG. 76.—Specimens of bones and fragments of bones left after the destruction of a body by boiling for an hour and a half in a solution of crude potash.

phalanx of the little finger) which were identified by experts for the state as being of human origin, but this was strenuously denied by experts for the defense. The chemical experts, however, for both sides (Delafontaine, Gibson, and Haines for the state, and Long, Wesener, and Riese for the defense) agreed substantially in regard to the following facts, which they established separately by numerous experiments:

An adult human body if placed in a hot or boiling solution of caustic potash of from 5 to 25 per cent. strength is readily disintegrated and practically all the soft parts are dissolved in from two to three hours. The hair is one of the first tissues to be dissolved, and the soft internal organs are easily attacked; the skin and muscles yield somewhat less readily, while the cartilages and tendons sometimes persist for a considerable

length of time. In nearly every experiment a small portion of soft tissue was found undissolved at the close of the operation. This seemed to consist of an aggregation of fibrous material, and its quantity depended largely on the strength of the alkaline liquid and the time and heat employed. At the most it amounted to only a small fraction of the body weight. During the disintegration of a body in boiling alkali a little soapy or ammoniacal odor is given off; this is slight, however, if the body is fresh, but is more pronounced if it is old and putrefactive decomposition has set in. The liquid resulting from the corrosion has a dark, reddish-brown color.

The bones were much less attacked than the soft parts, but in all cases were more or less disintegrated and softened. Many of them broke down into small flakes and fragments during the process of boiling, and the remainder crumbled upon being handled or upon moderate pressure. As a rule the small bones, as would be expected, were most completely disintegrated, while the large and hard bones, like the femur, the tibia, and the temporal bone, passed through the alkaline bath only imperfectly softened. It is a singular circumstance, however, that in nearly every experiment some of the small bones, such as those of the hands and feet, were almost certain to come out seemingly but slightly affected, while on the other hand occasionally the larger bones would be disintegrated in an unexpected manner. The bones after being taken from the alkaline bath and placed in a fire were found to be consumed and broken down into an unrecognizable mass in less than half the time that was required to produce the same effect with bones that had not been subjected to the alkaline liquid. A temporal bone, identified by Dr. George A. Dorsey, then of the Field Columbian Museum, as of human origin, was found in some ashes in front of the boiler. It evidently had passed through both the boiling alkaline bath and the fire under the boiler, and yet its form and markings were recognizable, although it crumbled upon even slight manipulation.

Articles of clothing made of wool or silk are easily attacked by the boiling alkali, but those of cotton or linen pass through almost unchanged. Artificial teeth and most of the metals are also unaffected, and this was a matter of much importance in the Luetgert case, the gold rings and artificial tooth before mentioned thus passing through the vat unacted on. The metal aluminum, however, is readily attacked and dissolved by alkaline fluids, a fact which was also of importance in the case, as the false teeth worn by the woman were supported on an aluminum plate which naturally entirely disappeared in the vat.

The jury disagreed on the first trial of the accused, but a second trial resulted in a conviction.

DEATH FROM POUNDED GLASS AND OTHER MECHANICAL IRRITANTS

BY WALTER S. HAINES, M. D.

CHICAGO, ILL.

SHARP-CORNERED or pointed objects, especially particles of glass, are popularly supposed to be an efficient means of producing death, and have been considerably resorted to, more particularly by the insane, for the purpose of suicide; they have also occasionally been administered with homicidal intent.

In the middle ages powdered diamonds were sometimes given for the purpose of inducing sickness or death.¹ The sharp, excessively hard angles of the diamond produced, or at least were supposed to produce, rapid and certain effect. Benvenuto Cellini, in his autobiography, states that an attempt on his life was planned by the administration of diamond dust; the man, however, to whom the diamond was given to pulverize, substituted for it a softer stone and no untoward effects were produced.

Although such articles are frequently spoken of as poisons, they are not such in the true acceptation of the word.² They are practically insoluble, and do not, therefore, enter the circulation. Their effects are not produced after absorption, but are purely mechanical and local. They do not, consequently, strictly come under the head of poisons, but are included in the expression "other noxious things" of the statutes.

While any object with sharp points or angles is capable of producing gastro-intestinal irritation, the article of greatest interest from a medico-legal standpoint is pounded glass, and this, therefore, deserves chief attention.

Pounded glass is commonly looked upon as extremely dangerous when taken internally, and is often spoken of as an efficient "poison." There can be no question that the ingestion of particles of glass of a certain size may lead to such injury of the mucous membrane of the stomach and intestines as to cause death. A number of cases are on record of its fatal use, and in Russia death from its criminal administration is said not to be infrequent.³ It is a favorite method of destroying certain of the lower animals, like dogs, rats, and mice, and its efficiency is said to have led to its extensive use by the official rat-catchers of Manila⁴ and of other Oriental cities in their war against the rodent propagators of the plague.

¹ Corner, Jour. Amer. Med. Assoc., 1919, 72, p. 514.

² See page 18 in section on General Principles of Toxicology.

³ Virchow's Jahresbericht, 1893, i, p. 505.

⁴ Med. Record, vol. lxiv, p. 25.

Still there can be no doubt that the dangers of broken glass and of other similar objects have been greatly overestimated. The results of experiments and the experience of professional glass-eaters indicate that they are far less dangerous than is commonly supposed. Glass suitably powdered has even been proposed as a remedial agent, Johns¹ claiming that it is an efficient vermifuge and, if properly pulverized, is harmless; and in some parts of Russia there is a popular belief that it is a valuable remedy in certain diseases. Death, however, has sometimes resulted from its use for this purpose.²

Observations made by the writer in conjunction with Dr. E. F. Ingals on a professional glass-eater are of interest in this connection. He was a strong young negro who claimed and appeared to be in excellent health. He gained a livelihood by exhibiting himself in cheap museums and at fairs as a glass-eater. He voluntarily placed himself in our hands for scientific investigation. On one occasion he ate, in our presence and at our office, the following articles, all being provided by us personally: half a dozen 6-inch test-tubes, two good-sized lamp chimneys, an ordinary 4-ounce medicine bottle, two pieces of window-glass, each 4 inches square, and three slips of colored glass each 1 inch wide and 3 inches long. In eating them he bit the glass off, chewed it up, and swallowed it much as if it had been any ordinary article of food. He asserted that he could distinguish by the taste glass of different colors, and it was for this purpose that the colored slips were given him. He was thoroughly blindfolded when he ate them, but he promptly indicated the color.

Before and after eating the glass the man's mouth and throat were carefully examined by Dr. Ingals with a mirror and laryngoscope. They were found perfectly normal except that the gums and inside of the cheeks were whiter and thicker than normal, and, after eating the glass, they were bleeding from a number of small cuts. The man was kept under observation for several hours after eating the articles mentioned, but he at no time showed the least unfavorable symptom. At the end of the first hour slight emesis was provoked by tickling the fauces. The vomited matter consisted of partially digested food mixed with a large number of fragments of glass and an excessive amount of thick mucus. The man admitted that he had eaten a hearty meal before submitting to the test, and that this was his custom before each exhibition. He died two or three years subsequently from a subacute gastro-enteritis, presumably from the irritation produced by his long-continued glass-eating.

Gracy³ reports another case of glass-eating very similar to the above, and the experiments of Lesauvage, published at Paris in 1810 in an inaugural dissertation,⁴ are of similar import. He states that $2\frac{1}{2}$ drams of pounded glass were given to a cat without injury, and that a dog took 6 or 7 ounces in eight days without suffering the slightest incon-

¹ Lancet, February 19, 1825, p. 217.

² Virchow's Jahresbericht, Loc. cit.

³ Med. and Surg. Reporter, 1888, lviii, p. 61.

⁴ Lesauvage, Recherches sur les effets du verre et des substances vitriformes portés à l'intérieur des organes digestifs.

venience, although care was taken to administer it while the animal was fasting and the fragments were frequently a line in length. He himself swallowed a considerable number of pieces, up to 2 mm. (0.08 inch) long, without producing any bad effect.*

Simmons and von Glahm¹ fed ground glass to a number of dogs for varying periods of time. The dogs were then killed and postmortem examinations made. As the result of their experiments, they state the following conclusions: "The ingestion of ground or powdered glass has no toxic effect and produces no lesion, either gross or microscopic, on the gastro-intestinal tract of dogs."

A consideration of such facts as the above has led some medicolegal authorities (compare the first case under Illustrative Cases, below) to question altogether the dangerous properties of pounded glass, forgetting the well-authenticated cases of serious sickness and death from the agent and overlooking the circumstance that, in the experiments of Lesauvage and of others in the same line, the largest pieces of glass administered were still quite small. After carefully examining the evidence concerning the subject we agree fully with the following conclusions reached by Marc² in regard to the question: "The observations which have been made on glass-eaters and the experiments of Caldani and Mandruzzato, which tend to demonstrate the harmlessness of substances of this kind, have been adopted too lightly by certain physicians. Caldani experimented on animals, and even, what appears difficult to conceive, on a young man of fifteen years, whom he caused to swallow powdered glass without his experiencing the least inconvenience. Mandruzzato repeated these same experiments on animals and on himself and obtained the same results. These observations, however, only prove at the most that powdered glass introduced into the stomach is not always harmful: and the above isolated facts do not demonstrate in any manner that in other cases and under other circumstances one or more sharp points applied to the interior walls of the alimentary canal may not produce a most serious mechanical action. It follows, moreover, from the fact that most glass-eaters die from intestinal affections³ and from several sudden deaths following the swallowing of glass⁴ that substances of this character may be dangerous."

It is probably true with glass, as with other mechanical irritants, that the effects differ widely with the size and form of the pieces ingested, with the sharpness of their edges and angles, with the amount and character of the food in the alimentary canal, with the structure and sensitiveness of the stomach and bowels, and with the character of the glass used—the edges and angles of some kinds of glass being much more rapidly attacked and dulled (and thus rendered less harmful) by the acids of the stomach than is the case with other kinds.

The organism seems to be endowed with an instinctive provision by

¹ Jour. Amer. Med. Assoc., 1918, 71, p. 2127.

² Manuel d'autopsie cadav. médico-lég., p. 61.

³ Plouquet, Sur les morts violentes.

⁴ Gmelin, Dans son histoire des poisons minéraux, and Metzger.

which it defends itself from threatened perforation by sharp articles. According to the observations of Exner,¹ when a sharp object approaches the wall of the intestine, the latter retreats from it, forming a sort of dimple which receives the sharp projection and prevents injury to the mucous membrane. Foreign bodies of this character are arranged by the action of the muscular walls of the intestine so that they lie with their longest axis parallel to the long axis of the section of the bowel in which they are situated, and thus the chance of injury is reduced to a minimum.

Mode of Action.—Sharp-cornered articles may act in several ways: First, the piece may cause perforation of the wall of the stomach or bowel, with the usual consequence of such perforation. Owing, however, to the defensive actions on the part of the intestine, spoken of above, perforation by such articles is relatively rare. The effects of perforation vary according to the size, shape, and character of the perforating body, as well as with the location in which the perforation occurs and the condition of the patient as to resisting power, etc. It is not uncommon to have needles penetrate the wall of the bowel without any noticeable results. If a perforation can be shown to have caused death, the presence of glass in the stomach or intestines or in the peritoneal cavity would raise a strong presumption in favor of the glass being the cause of death.

Second, the action of a large number of pieces may set up a widespread irritation and inflammation, arising from the subsequent local infection, causing an acute or subacute gastro-enteritis, and this is probably the chief cause of suffering and death produced by these articles. It seems likely that in the case of professional glass-eaters the repeated wounding of the mucous membrane may have led to some sort of immunity which prevents an infection that might easily occur in other persons. The impunity with which these persons swallow such articles can hardly be urged against the possibility of death being produced in other persons. Especially the enfeebled condition of age or the presence of disease may render infection of slight wounds fatal. Before sickness or death, however, is attributed to the irritation caused by powdered glass, it should be shown that the other more usual causes of gastro-intestinal inflammation were absent and that the glass was administered in sufficient quantity and in particles of sufficient size to produce great irritation.

Third, a wound produced by a piece may become infected, and the infection spreading to other organs or involving the general system may be fatal, and this is probably the cause of trouble in some cases. If evidence can be produced to show that the death arose from a remote infection proceeding from a wound of the gastro-intestinal mucous membrane, the presence of glass in the stomach or intestines would make it probable that it was the noxious agent. Here also immunity, original or acquired, may play a part.

Symptoms.—The symptoms produced by swallowing broken glass are generally due to irritation of the mucous membrane of the stomach

¹ Arch. f. d. ges. Physiol., vol. lxxxix, p. 253.

and intestines, and are consequently similar to those of gastro-enteritis produced by other agencies. They may vary in intensity from those cases in which but little inconvenience is felt to those attended with the most intense suffering. There is generally sharp pain in the stomach and later in the intestines, and sometimes nausea and vomiting, the vomited material usually being streaked with blood. The bowels are generally constipated, but sometimes there is diarrhea, the passage of stools being attended by pain and the material passed is usually mixed with blood. In case of perforation of the stomach or intestines collapse usually supervenes and the patient soon dies.

In a case reported by Blake¹ a girl of sixteen, with suicidal intent, took a teaspoonful of broken glass mixed with bread. The next morning sharp cutting pains began to be felt, which were paroxysmal in character and referred to the epigastrium and later to the neighborhood of the umbilicus. When seen by the physician she was delirious from the pain, which required a hypodermic of morphin for its relief. There was great tenderness over the abdomen, which was somewhat swollen. The teeth chattered, the skin was hot and dry, the mouth and lips were parched, and the tongue clean, but very dry. There was excessive thirst; the pulse was 112 a minute and the temperature 99° F. The pain and tenderness continued for four days, when she had a copious stool following an injection of oil. The dejection was accompanied by pain and the passage of blood. The stool contained about a dozen large fragments of glass and a larger number of smaller pieces. From this time there was gradual improvement, and the patient was discharged from the hospital on the thirteenth day.

If the patient survives the immediate effects of the irritant, a subacute or chronic gastro-enteritis may follow which may last for weeks or months.

Fatal Dose and Fatal Period.—It is impossible to state what the fatal dose of broken glass is. As has already been pointed out, persons may take large quantities of the substance without any seemingly harmful results. On the other hand, smaller quantities may possibly produce great irritation and possibly perforation and death. Very much depends on the condition of the stomach, as to the presence or absence of food, upon the size and sharpness of fragments of glass, and on individual susceptibility. There is no doubt that a teaspoonful of pounded glass would in most cases be capable of producing serious effects, especially if the particles were of considerable size and presented numerous sharp angles; but the same quantity if finely pulverized might usually be taken with little or no effect. In a case reported by Hebb² a large teaspoonful of pounded glass caused the death of a child of eleven months.

Nothing can be said definitely in regard to the fatal period. The patient may die from perforation of the stomach or bowels or from acute gastro-enteritis in a day or two, or he may linger with subacute

¹ Boston Med. and Surg. Jour., 1871, lxxxiv, p. 191.

² Midland Med. and Surg. Reporter, 1829, i, p. 47.

or chronic trouble for many days or weeks, and finally die from the remote effects of the irritant. In a fatal case reported by Reichardt¹ death occurred six days after taking the powdered glass.

Treatment.—If the case is seen early, an effort should be made to evacuate the stomach. This, however, cannot generally be accomplished by the stomach-tube or pump on account of the choking of the tube by the particles of glass. Resort must be had, therefore, to emesis, which is best produced by tickling the fauces or by hypodermic injection of apomorphin. There is some objection, however, to this treatment, for, in the act of vomiting, particles of glass may cut the walls of the stomach and of the esophagus; we believe, however, that, on the whole, it is better to evacuate the stomach even though there is some risk attending it. After evacuating the stomach, considerable quantities of bread, potatoes, or other similar food should be given to form a soft envelop for the pointed particles. If the bowels do not move, an injection of a mucilaginous or oily material should be used.

Pain should be treated by the use of opiates and hot applications, and collapse guarded against by the external use of warmth and the internal administration of cardiac and general stimulants, such as small doses of alcohol, ether, ammonium carbonate, and strychnin.

If the symptoms point to perforation of the stomach or bowels, a surgical operation should be promptly resorted to, with the hope of averting what would otherwise almost certainly be fatal.

Postmortem Appearances.—These are such as are commonly observed in cases of gastro-enteritis and are found almost entirely in the gastro-intestinal tract. There is redness of the mucous membrane, which is covered with tenacious mucus and frequently streaked with blood. Perforations in the stomach and intestines should be carefully looked for, and in case they are found the abdominal cavity should be searched for particles of glass which may have escaped into it.

Hebb² gives the following account of the postmortem appearances in the case of an infant destroyed by the administration of roughly pounded glass: All the organs, including the large and small intestines, were normal except the stomach, which “was lined with a thick layer of tenacious mucus, streaked with blood, and it required to be peeled off before the villous coat beneath could be exposed to view. This last was in a state of amazing vascularity; it presented one entire congeries of vessels; numberless particles of glass, some large and some small, were adhering to it, and in many places it was lacerated by them.”

In Reichardt's case³ erosions were found in the pharynx, stomach, duodenum, and upper part of small intestines; and in the case of a boy of twelve years, described by Bronowski,⁴ many ulcers were found on the mucous membrane of the stomach and intestines, and in both organs the powdered glass was discovered in a form resembling sand.

¹ Arch. d. Pharm., second series, vol. xci, p. 9.

² Loc. cit.

³ Loc. cit.

⁴ Virchow's Jahresbericht, 1893, i, p. 505.

In making the postmortem examination unusual care should be exercised to determine the existence of wounds and to ascertain the situation of any pieces of glass that may be present in the stomach or intestines. In case of a legal investigation, much may depend upon these points in determining whether death occurred from the glass or possibly from other causes.

Chemical Examination.—The contents of the stomach and intestines and vomited matter and feces may be washed in a stool-sieve and any particles left on the sieve examined as directed hereafter. If the amount of food, however, is great or the amount of glass small, it is better to destroy the organic matter by treatment with hydrochloric acid and potassium chlorate by the process of Fresenius and Babo, as described on page 46 in the section on General Principles of Toxicology. After the destruction of the organic matter the material should be strained and particles of glass looked for in the residue. If metallic articles, such as tacks, needles, and pins, are to be searched for, the acid and chlorate are inadmissible and should be replaced by a strong solution of potassium hydroxid.

Particles of glass found by any of these methods should be carefully measured. They may be identified as glass by the following properties and tests: (a) They are transparent or translucent; if the glass, however, has an exceedingly irregular surface, this property may be largely lacking. (b) The surface is more or less irregular, with sharp, uneven angles, by which it may be distinguished from regularly crystalline bodies. (c) It is fusible when heated on platinum foil; sand or other forms of silica do not fuse. The globules adhere to the foil and may show sufficient transparency for lines to be seen through them and even for the reading of letters. (d) It is ductile. (e) When glass is heated in a platinum dish with hydrofluoric acid it dissolves and the silica disappears, leaving a residue consisting of the fluorids of the metals from which the glass was made. Quartz or silica, for which glass might be mistaken, would disappear wholly under this test. The examination of this residue for metals may show the original composition of the glass.

In the examination the greatest care must be taken that the material shall not be contaminated by pieces of glass accidentally derived from vessels or other apparatus. The discovery of a few pieces of glass in the stomach may sometimes be due to the accidental swallowing of pieces of glass from glass vessels in which food has been contained.

In an alleged case of criminal poisoning by glass, tried a few years ago in New Jersey, Dr. John Marshall¹ demonstrated that the fragments of glass found in the organs of deceased, upon chemical examination, could have been introduced by the screwing down of the cover of the Mason fruit jar in which the organs were sent to the chemist. Splintering of small pieces of glass in the use of fruit jars is by no means uncommon.

Small pieces of glass are occasionally found in food from accidental

¹ Personal communication.

contamination. Simmons and von Glahm¹ report that of 120 specimens of food submitted to them for examination, particles of glass were found in 17; in 13 of these it was evident that the glass was accidentally present.

ILLUSTRATIVE CASES

Beck² reports a case that occurred near Bayeux, France, in which the accused was supposed to have murdered his wife with pounded glass. A quantity of this substance was found at the autopsy in the stomach and intestines, and these organs presented signs of marked irritation. Professors Baudelocque and Chaussier, who were called in to give testimony in the case, gave it as their opinion, after thoroughly considering all that had been written on the subject, that pounded glass is not dangerous, and suggested that the glass found in the stomach might have come from some vessel of that material being broken by the deceased's teeth during the convulsions which preceded her death. The accused was acquitted.

Dr. W. Turner, of Spanishtown, Jamaica, relates that an attempt was made by a negro woman to "poison" a family of seven with pounded glass. A large quantity of the pounded glass was put into a dish of curried fowl, of which every one ate freely. The presence of the glass being discovered toward the conclusion of the meal, the head of the family immediately administered purgatives. In consequence they all passed large quantities of coarsely powdered bottle-glass. When Dr. Turner saw them four days after the attempt none of them had suffered any inconvenience.³

Portal⁴ records a case in which a young man broke his drinking-glass with his teeth and swallowed the pieces. Frightful pains in the stomach and convulsive movements followed. Portal, who was called in as a physician, ordered the patient to eat much boiled cabbage to envelop the glass and then take an emetic, whereat many pieces of glass were thrown up. The patient then received milk, warm baths, and enemata, but in spite of this became emaciated and had to be kept on a milk diet for four weeks before he recovered.

Foderé,⁵ arguing for the dangerous properties of pounded glass, mentions a case of a man who introduced a liqueur glass into his rectum. A surgeon, in endeavoring to remove it, broke it and was unable to extract one of the fragments. The latter caused intense pain, and produced several fistulous abscesses and extensive gangrene, and finally death. The author concludes with the question: "Would the evil results have been less if a piece of glass had remained in the stomach or any other part of the alimentary canal?"

At the trial of Mrs. Mary B. Sanderson, accused of killing her husband by feeding him ground glass in oatmeal, held in Marshall, Mich., December 19, 1899, F. F. Stevenson testified to having himself

¹ Jour. Amer. Med. Assoc., 1918, 71 p. 2127.

² Medical Jurisprudence, 3d ed., p. 507.

³ Edinburgh Med. and Surg. Jour., 1824, xxii, p. 225.

⁴ Arch. d. Pharm., second series, vol. xci, p. 9.

⁵ Traité de médecine légale, vol. iv, p. 113.

caten ground glass without harm or inconvenience and also to having administered it to dogs without causing any injury. He exhibited pieces of glass from $\frac{1}{4}$ to $\frac{1}{2}$ inch in length which had passed through the



FIG. 77.—Seventy-four grams of glass extracted from the stomach (Halsted).

alimentary canal of a dog without inconvenience to the animal. Dr. John E. Clark, Professor of Chemistry in the Detroit Medical College, gave similar testimony. Professor A. B. Prescott, who made the

examination of the organs for the State, found five pieces which he recognized as glass by their transparency, their fusibility, their angular outline before fusion, and their globular character after fusion. The largest of these pieces was a little more than 2 mm. (0.08 inch) in diameter, the others ranging from $\frac{1}{2}$ to $1\frac{1}{2}$ mm. The deceased, who was eighty years of age, had been suffering for several weeks with diarrhea, the passages being tinged with blood. The accused was acquitted.

Marcet¹ reports the case of a sailor who was accustomed to swallow knives and other sharp objects; upon postmortem examination some thirty knife-blades were found in his stomach, but no evidence of recent or old ulcers.

Credé collected 26 cases in which the stomach had been opened for the extraction of foreign bodies, and Fricker² added 27 more. The latter reports a remarkable case of a woman who, in several attempts at suicide, swallowed numerous foreign bodies. He removed from her stomach 37 articles, including 1 key, 2 teaspoons, 1 fork, wire nails, 2 hairpins, 9 sewing needles, 12 pieces of glass, etc. After the removal of these bodies the patient made a rapid recovery. Some of these articles had remained in the stomach for three months.

Meissenbach³ extracted a large number of articles, including an ounce of broken glass (electric-light globe), from the stomach of a professional glass-eater who styled himself "The Human Ostrich." Although he had swallowed glass and other foreign objects for a number of years, he had experienced no inconvenience until shortly before the operation was performed.

W. S. Halsted⁴ reports a case in which he extracted from the stomach of a professional glass-eater, who had been induced by some medical students to swallow a large number of foreign articles, 74 gm. (1142 gr.) of broken glass (Fig. 77), and 208 articles consisting of 28 pieces of chain, 99 nails, and 81 screws, knives, tacks, pins, etc.

Another case similar to the above has been reported by G. F. Inch.⁵

Ollivier records⁶ the case of an infant two and a half months old who was given some pins by his nurse, who was accused of trying to murder him. The child passed the pins *per anum* and his health was not seriously affected. The accused stated that she acted under morbid impulse due to menstruation, and she was acquitted. Ollivier concludes that although pins or needles when swallowed may cause death, they seldom do so. A case is cited by him, however, in which an infant died from the effect of a needle which perforated the wall of the stomach.

For an additional case of poisoning by glass see Allgemeine Wiener Med. Zeitung, 1863, viii, p. 254.

¹ Medico-Chir. Trans., vol. xii, p. 72.

² Deutsch. med. Wochenschr., 1897, No. 4, p. 56.

³ Jour. Amer. Med. Assoc., March 5, 1898, p. 513.

⁴ Contributions to the Science of Medicine, p. 1047; the Johns Hopkins Press, 1900.

⁵ Amer. Med., April 12, 1902, p. 603.

⁶ Ann. d'hygiène, 1839, xxi, p. 178.

MEDICOLEGAL EXAMINATION OF BLOOD AND BLOOD-STAINS¹

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IN cases of homicide articles to be submitted for medicolegal examination may naturally be numerous and varied, and it is always the duty of the officers to collect all substances that contain suspicious stains and transmit them to the expert.

Everything that appears in the least degree suspicious should be taken, such as articles of clothing or bedding, substances containing suspicious stains found in the neighborhood of the deceased, on the person of the accused or suspected, and any implements or weapons that may possibly have any connection with the case. The greatest care must be taken to preserve, beyond any possible doubt, the identity of these substances, some of which afterward may have to be taken to court as *corpora delicti*. They must, therefore, be kept in sight, or under lock and key, until they are delivered to the expert, and this delivery may have to be made in person, as it is sometimes impossible to preserve the identity of packages when sent by express, owing to the breaking of the seal or accidents of various kinds. It is important always to bear in mind that in capital cases the identity of all substances submitted to medicolegal examination must be established *with absolute certainty*, and that every precaution must be taken to insure this result.

After all suspected substances have been delivered to the expert, he then, is responsible for the preservation of their identity until he delivers them in court, or in special cases to officers on written order of the proper court official. The expert must keep all the substances in his possession under lock and key when they are not within his field of vision. The expert first makes a careful preliminary examination of all substances that have been submitted. This examination should be made not only by the unaided eye, but also by means of magnifying-glasses, both by daylight and by artificial light, since it often happens that small blood-stains can be detected much more readily by artificial light than by daylight. Every spot that appears suspicious should be described and located, and its nature afterward determined by chemical tests or microscopic examination. Each article received should be carefully described, together with the detailed statement of the results of the preliminary examination in each case.

¹ This article, in its present form, is a revision and expansion of that appearing in the first edition and written by the late Dr. Edward S. Wood.

The most important kinds of stains submitted for medicolegal examination are:

1. Blood-stains.
2. Stains containing blood, such as menstrual, lochial, and nasal, after epistaxis.
3. Seminal stains, as in cases of alleged rape, adultery, or sodomy.
4. Stains containing mucus or pus, such as nasal, leukorrheal, and gonorrheal.

BLOOD-STAINS

The expert is more frequently required to examine stains for blood than for anything else, and he is requested to determine, in the first place, whether the stain is a blood-stain or contains blood or not. Second, if a blood-stain, whether the blood came from a mammal or from a bird, fish, or reptile. Third, if the blood is mammalian, is it that of any given species of mammal. It is often alleged by the accused in cases of homicide that the blood-stains in question were made by the blood of a fish, bird, reptile, or other animal. In such cases the work may be narrowed down to determining whether the blood in the stain is consistent with that of the animal mentioned, or consistent with its being human blood. When no data are given, the expert must give the result of his investigation, and state whether or not these results are consistent with the staining being that of human blood.

There are also other questions that the expert may be required to decide in cases in which there is no doubt that the blood in the stain is human, as, for instance, in the case of blood-stains or pools of blood found in the immediate neighborhood of the victim of a homicide. It may be possible to determine approximately the length of time that has elapsed between the escape of the blood and the finding of the body from the observation of blood-stains. Again, an opinion is often requested concerning the direction from which the blood must have come in order to have produced a given stain. In order to throw light on these questions it is necessary to understand some of the physical and chemical properties of blood.

The blood is composed of a pale, straw-colored fluid having a specific gravity of about 1028. In this fluid are suspended the red and the white blood-corpuscles, and the blood-plates, which, up to the present time, have no medicolegal importance. After the escape of blood from the vessels coagulation occurs and the blood-serum is the clear, limpid fluid that exudes from the clot. It consists of a solution in water of various protein substances, and of several inorganic salts, the principal one of which is sodium chlorid. The constituents of the blood-serum have a primary importance in the medicolegal examination of blood in connection with the serum, precipitin, or biologic test (see p. 927).

Of the solid constituents of the blood, the red blood-cells are the only ones that at the present time are of practical value medicolegally. They contain the hemoglobin and impart the red color to the blood. The difference in the color of arterial and venous blood is due to the

varying proportion of oxygen held in combination with the hemoglobin. The number of the red cells in the blood varies in different animals and in different individuals. The number varies somewhat in different persons in health, and in some diseases the number differs greatly from the normal. Authorities agree that the average number of the red blood-cells in the blood of healthy adult human beings is from 4,500,000 to 5,000,000 in a cubic millimeter. Wormley has calculated, estimating the number as 5,000,000 a cubic millimeter, that 1 grain of human blood contains 825,000,000 red cells, and, therefore, that the weight of a single red cell is approximately $\frac{80000}{100000000}$ grain. The blood of the rabbit contains about 3,500,000 red cells in a cubic millimeter, and that of the goat about 18,000,000 in a cubic millimeter.

The white cells exist in healthy human blood to the extent of about 7000 a cubic millimeter. Although their proportion to the red blood-cells in health is about 1 to 700, in some diseases their relative proportion may be much in excess of this, and in rare instances may be increased even to the proportion of 1 white to 2 or 3 red cells. As yet, however, they have no practical value in the usual medicolegal examination of blood-stains.

The **coagulation of blood** is of importance in certain medicolegal cases. It is well known that when blood is drawn into a dish and allowed to stand, it separates into two portions—a solid mass, the clot or coagulum, red in color and containing all the solid elements of the blood, and a nearly colorless liquid portion, the blood-serum. The time required for the complete coagulation of the blood differs in different animals, and under different circumstances the time required may differ in blood from the same animal. For instance, the blood of the fowl begins to coagulate in one and a half minutes; that of the rabbit, sheep, and pig in from a half to one and a half minutes; that of the horse and ox in from five to thirteen minutes; that of the dog in from one to three minutes; that of man in from three to four minutes and is complete in human blood as a rule in from nine to ten minutes. In the case of bird blood, coagulation is rapid and the coagulum large, while in cold-blooded animals the coagulation is slow and the coagulum small.

The following circumstances increase the rapidity of the coagulation: Increase of the temperature; exposure of a large surface of blood to the air—as, for instance, when it is collected in a shallow dish; contact with numerous points of some foreign body, as when stirred or beaten with a number of wires, or, as in the case of many stains submitted to medicolegal examination, when a small drop falls on a rough surface. The following conditions may delay, or even prevent, coagulation: Exposure to cold, as, for instance, if cooled rapidly to the freezing-point, coagulation will not take place for an hour or so; contact with oily or greasy substances; admixture with syrupy liquids; and heating the blood quickly to a temperature of 56° C. (132.8° F.) entirely prevents coagulation.

The blood is a viscid fluid, and this viscosity often renders it possible to determine in certain blood-stains the direction from which the blood

must have come. When a minute drop of blood strikes an object after having been propelled from an artery, it forms an oval- or pear-shaped stain if the surface against which it impinges be more or less oblique, and the bulk of the blood is driven to the farther end of the stain; the same results may follow the force of a blow caused by some blunt instrument, such as a club, striking in a pool of blood. If, however, the surface against which the blood impinges be vertical and of such a nature that it does not immediately absorb the blood, then the bulk of the blood, which has been driven to the farther part of the stain, will, if the blood came from below upward, gravitate back to the lower portion. If the surface happens to be a rough one, like that of a shaggy



FIG. 78.—Showing direction from which the blood came.

overcoat cloth, the coagulation takes place so rapidly that this gravitation does not occur, so that, if a drop of blood be propelled from near the surface of the ground upward against the surface of a rough overcoat, that surface being vertical, it will be found on examination after the stain has become dry that the bulk of the blood is in the upper portion of the stain, which is generally the smaller end. The importance of being able to determine the direction from which the blood came in order to form the stains found in certain cases is self-evident and needs no further discussion. Figure 78, reproduced from a photograph, shows the points mentioned.

Drying of Blood.—The time required for blood to dry is also important. For instance, in a case of double murder the appearance of

the blood beneath the two bodies showed that a considerable length of time must have elapsed between the deaths of the two individuals. A drop of blood dries much more slowly than a drop of water of the same size. The character of the surface on which the blood falls also has considerable bearing on the time required for the complete drying of the blood. If the surface be an absorbent one, so that the blood may permeate the substance itself, as in the case of a piece of unstarched cotton or linen cloth, the drying takes place quite rapidly, but if the surface be a non-absorbent one, like that of a piece of glass or a board having a smooth surface, and also in the case of some kinds of dense woven fabrics, the time required for the drying of a drop of blood is much greater than that of a drop of water of equal size. A large drop of blood requires proportionally a longer time to dry than a small drop. For instance, a drop of blood allowed to fall from the end of a finger on a piece of glass, the drop measuring $\frac{3}{8}$ inch in diameter, required one hour and five minutes for complete drying under favorable conditions—namely, in a room with an open fire and a temperature of 71° F. (21.6° C.). A drop of similar size on a piece of soft pine board in a room in which the temperature was only 65° F. (18.3° C.), and with the atmosphere not so dry as in the previous instance, did not undergo any perceptible change for half an hour, and in one hour it had only begun to shrink and have a glazed appearance on the edge. This glazed appearance gradually extended toward the center of the drop, and the drying became complete in exactly two hours. Therefore, from one to two hours is required for a single drop of blood to become dry.

These facts show how necessary it is carefully to observe every blood-stain in the medicolegal cases submitted for investigation. The number, exact location, shape, color, and whether or not the individual stains have a different density in different parts must be noted. From the facts obtained by simple inspection, which should be made as quickly as possible after the receipt of the substances to be examined, important information may possibly be gained with reference to the age of the stain, the direction from which the blood emanated, and perhaps some idea of the force with which it was propelled.

Color of Blood-stains.—If a blood-stain be recent, it can sometimes be determined, within narrow limits, by carefully observing its color, how long a time has elapsed since the stain was made. A freshly made blood-stain, after it has become dry, under ordinary circumstances has a bright scarlet color. Upon exposure to ordinary daylight this color gradually changes to a dull brown during a period of about ten days, after which time the color does not change materially; therefore if a given stain has been exposed only to light and air under ordinary conditions for less than ten days, some opinion can be formed as to the approximate age of the stain. It must be borne in mind, however, that there are some conditions that hasten this change of color: continuous exposure to direct sunlight; the application of a high degree of heat, such as might be obtained by a hot iron or the heating of the substance containing the stain on a stove or in an oven; or treating the stain

with certain preservatives, like alcohol, naphtha, or formalin, will very rapidly produce the change of color to a dull brown.

Solubility of Blood-stains.—In case of recently shed blood on clothing or weapons, an extract can be made with salt solution or distilled water. When the stain has been exposed to heat or chemicals, the extraction takes a long time and it may be necessary to use some other solvent. Katayama¹ found that blood-stains dried in porcelain dishes and exposed to a temperature of 80° C. (176° F.) for an indefinite length of time or to 100° C. (212° F.) for an hour, were still soluble in distilled water within twenty-four hours; if heated to 140° C. (284° F.) for one hour the stains were soluble only in caustic potash of a specific gravity of 1.017 diluted with 3 volumes of water just before use, or in glacial acetic acid. If the stain was exposed to 135° to 143° C. (275° to 289.4° F.) it lost its power of reacting to the guaiac or Van Deen test and if exposed to over 145° C. (293° F.) it lost its power to form Teichmann's crystals. Sutherland² obtained very little extraction with a potassium cyanid solution in the case of stains heated to 140° C. (284° F.) for two hours, but he obtained crystals of hematin chlorid in extracts made with glacial acetic and concentrated sulphuric acid. Ferrai found that blood exposed to a temperature of 130° C. (266° F.) for an hour, 140° C. (284° F.) for twenty minutes, or 160° C. (320° F.) for five minutes, yields an extract with which the serum reaction cannot be obtained. If the stain has been exposed to formaldehyd the solubility is greatly altered, rendering Pfaff's scale unreliable. This scale is based on the solubility of the blood in a solution of arsenious acid, 1 : 120. Fresh blood dissolves at once; blood two to three days old, within fifteen minutes; three to eight days old, within thirty minutes; two to four weeks old, within one to two hours; four to six weeks old, within three to four hours, and blood a year or more old dissolves in from four to eight hours.

To extract a stain, scrape off a fragment if the stain be on a hard surface as of wood or metal, the particles being allowed to fall on a piece of white paper. If the stain be on cloth, a portion of the stained part and a portion of the unstained part, very essential in colored fabrics for control, should be removed and cut into small pieces. Then small particles of the stain or parts of the cloth are placed in a small test-tube of about 2 c.c., adding about 1 c.c. of salt solution, and stirred with a clean glass rod. This will give sufficient solution for the chemical and spectroscopic tests. For the precipitin test the extract must be filtered or centrifuged to obtain an absolutely clear solution.

Many substances resembling blood-stains are found on articles submitted by officials. Iron rust and stains of red paint containing iron seldom present a glazed appearance, but may be confusing on clothing until a chemical examination reveals the presence of iron. The rust or paint stains are not soluble in the usual solvents, but may be dissolved in warm hydrochloric acid.

The addition of a drop of potassium ferrocyanid yields the Prussian

¹ Vrtljschr. f. gerichtl. Med., 1888, 49, 269.

² Blood-stains, 1907, 6.

blue reaction in the presence of iron. This test should be made with unstained parts, especially in case of garments, as salts of iron are frequently employed as mordants. The addition of ammonia to the stain extract changes the reddish hue of vegetable coloring matters to a greenish crimson or bluish black, while blood pigment remains unaltered. Red or reddish-brown stains due to anilin dyes become yellow on the addition of nitric acid, while blood-pigment does not undergo such change in color.

METHODS OF IDENTIFYING BLOOD-STAINS

The methods employed in the identification of blood-stains are: (1) Chemical; (2) optical; (3) microscopic examination; (4) the precipitin, biologic, or serum test.

The chemical and optical methods are used for the purpose of detecting hemoglobin or its decomposition products. They serve also to detect the protein contained in the stain, but these tests do not enable us to distinguish between proteins of different species.

The detection of the hemoglobin, however, shows us with certainty the presence of blood, but since hemoglobin is contained in the blood of many animals, its detection throws no light upon the nature of the animal from which the blood in any given stain came. To determine this latter question resort is had to the microscopic examination of the blood-cells in the stains and especially to the precipitin test. By means of these methods of investigation it is usually possible to determine whether the blood is of human or animal origin. As pointed out on p. 928 hemoglobin may have antigenic properties and it is possible that use may be made thereof in the identification of blood.

Hemoglobin and its Decomposition Products.—Hemoglobin is the red coloring-matter of the blood, and is found in the blood of all the vertebrates with the exception of two, *amphioxus* and *leptocephalus*, and in that of many of the invertebrates. It carries the oxygen to the tissues, and with oxygen it forms two compounds, oxyhemoglobin and methemoglobin. In oxyhemoglobin the oxygen is loosely combined with the pigment and separates from it easily, while in methemoglobin the combination is much more stable. Solutions of oxyhemoglobin have the bright cherry-red color seen in arterial blood, while the darker color of venous blood is that of a solution of hemoglobin largely deprived of its oxygen. The color of a solution of methemoglobin is brown. Solutions of these three substances when examined with the spectro-scope show different absorption bands, which will be spoken of shortly.

Hemoglobin contains iron; it also forms distinct compounds with nitric oxid (N_2O_2) and carbon monoxid, the solutions of which give characteristic absorption spectra. The carbon monoxid hemoglobin has medicolegal importance in cases of poisoning by illuminating gas¹ and by the fumes from burning charcoal; poisoning by illuminating gas is common, owing to the large percentage of carbon monoxid in illum-

¹ See chapter on Gaseous Poisons.

inating gas. It is this compound that imparts the bright cherry-red color to the blood and tissues in cases of poisoning by this gas.

Hemoglobin is quite easily decomposed by various agencies. If a solution of it be heated to boiling, the color changes to a brown, due to the decomposition of the hemoglobin into a brown pigment—hematin—and a protein—globin. This pigment hematin is quite important medicolegally because it may be formed from hemoglobin by many agencies to which blood-stains may be exposed, and also because it is formed during some of the principal chemical tests for blood.

Hematin contains all the iron of the hemoglobin from which it was derived. It is insoluble in water, alcohol, and ether, but is soluble in alkaline hydroxids and in alcohol containing sulphuric acid. Solutions of hematin give characteristic absorption spectra. If a solution of hematin be treated with ammonium sulphid or some other reducing agent, a pigment called hemochromogen is formed; this pigment was formerly designated reduced hematin.

Another decomposition product of importance in medicolegal examination of some blood-stains is hematoporphyrin, or iron-free hematin. This pigment is produced from hemoglobin or hematin by the action of agencies that remove the iron from these compounds; some of these agencies are conditions to which blood-stains may be subjected accidentally or intentionally, as has been shown by Liman, Kratter, and Hammerl.¹ When this decomposition has taken place in a blood-stain, the application of the ordinary tests will not reveal the presence of blood-pigment, and it becomes necessary to resort to special methods for the recognition of the hemochromogen or the hematoporphyrin by means of the spectroscope.

If blood-stained articles be treated with naphtha or benzene, or certain deodorizers or disinfectants, the blood-pigment will be so decomposed that it cannot be detected by the ordinary chemical tests. At the same time the red blood-cells will be fixed to such an extent that they resist subsequent treatment with water.

Chemical Tests for Blood.—The principal chemical tests for blood are the following:

1. Teichmann's, or the hemin, test.
2. Sodium tungstate test.
3. Guaiacum test.
4. Benzidin test.
5. Phenolphthalin test.
6. Protein tests.

Teichmann's Test.—This is by far the most important test for blood-pigment, and is extremely delicate. It may be made in the following manner:

If a dried blood-stain, a small fragment of the dried blood should be removed from the stain with the point of a knife and transferred to a glass slide. If the stain be a diffused one, or if the blood, while still fresh, has soaked into the fabric, as in the case of a stain on cotton

¹ Vrtljschr. f. gerichtl. Med., 1892, 4, 41, 62.

or linen cloth, then it suffices to scrape a small portion of the stain with the knife-point, collecting the dust thus removed on a glass slide. The fragment of dried blood or the dust should then be treated on the slide with a small drop of water in which has been dissolved a minute fragment of sodium chlorid. This drop should then be evaporated to dryness by gentle heat, the dried residue covered with a cover-glass, a drop of glacial acetic acid allowed to run under the cover-glass, and the slide again gently heated until bubbles of gas are seen to form in the liquid under the cover-glass. This shows that the glacial acetic acid has been heated to the boiling-point. If, now, the slide be allowed to cool, the microscope will reveal the characteristic crystals of chlorid of hematin in case the stain examined contained blood. These crystals of chlorid of hematin are called "hemin" crystals, and they have a characteristic form.

The normal hemin crystals have a yellow to chocolate-brown color, and separate in the form of small rhombic plates. They naturally



FIGS. 79, 80.—Hemin crystals (common forms) ($\times 750$).

vary a little in size according to the rapidity of their formation. Sometimes two or more arrange themselves in the form of a cross or a rosette. Sometimes, particularly if the fragment of dried blood on the slide was of considerable size, the form of the crystals in some parts of the preparation may be somewhat modified, some assuming a pointed, oval shape, and in some the outlines may be a little irregular; in all cases, however, a sufficient number of the normal perfect crystals will be seen to render their identification positive. Figures 79 and 80 from photographs taken of different portions of the same slide, show this variation.

This test depends on the principles, first, that hematin is formed from the decomposition of the hemoglobin by heat, and, secondly, that the hematin in solution in boiling glacial acetic acid unites with the chlorin of the salt to form chlorid of hematin, which is soluble in boiling glacial acetic acid, crystallizing from this solvent on cooling.

Precautions.—Care should be taken in heating the slide not to raise the temperature so high as to decompose the hematin in the first

dry residue obtained. If the temperature be raised to about 142° C. (287.6° F.), no hemin crystals will be formed.

Further, on heating the slide after the addition of glacial acetic acid, the temperature should not be raised so high as to produce active boiling of the acid, since active ebullition may carry all the pigment beyond the edge of the cover-glass, which might prevent the detection of the hemin crystals.

The hemin test will not detect blood-pigment in blood-stains that have been heated to a high temperature, that have been subjected to the prolonged action of naphtha, solution of aluminum chlorid, or bromochloralum, or that have been exposed for a long time to direct sunlight.

Wachholz¹ found that all concentrated mineral and organic acids may be used for the test, and recommends that a 1 : 10,000 solution of concentrated sulphuric, lactic, or glacial acetic acid in 90 to 95 per cent. alcohol be used, as they boil easily and the crystals are not destroyed by excessive heat. Two drops of a 34 per cent. hydro-bromic acid in 5 c.c. of formic acid give colored crystals which stand out more prominently than when sodium chlorid and glacial acetic are used.

The Sodium Tungstate Test.—This test is of great value in the case of diffused blood-stains caused by the action of water on the original stain, as in unsuccessful attempts to wash a blood-stain from cloth, and in cases in which the blood exists in solution in water or some other aqueous fluid, such as urine. By means of this test all the blood-pigment is precipitated from its aqueous solution, and thus concentrated to a small volume in the form of a precipitate that can be tested by the hemin test or subjected to spectroscopic examination.

In the case of a diffused blood-stain in which the blood-pigment has been largely diluted with water and spread over a large surface of cloth or other fabric, the application of the hemin test in the ordinary way will generally fail to detect the blood-pigment. It is, therefore, necessary first to remove all the blood from a considerable piece of the cloth, concentrate to a small volume, and identify it by one or more of the other tests. This is best done in the following manner: A piece of the cloth of sufficient size—the amount required depending on the extent to which the blood has been diluted, this being determined generally by simple inspection—is removed and placed in an evaporating dish or wineglass containing distilled water in which has been dissolved a crystal or two of potassium iodid. In this the fabric is soaked out and frequently stirred and pressed by means of a glass rod, so as to facilitate the thorough washing out of the pigment from the cloth. The fluid should be poured off into a flask or test-tube, according to the amount used, and the process repeated once or twice with fresh portions of water and potassium iodid, and finally the fluid entirely pressed out from the cloth. These united washings should then be filtered so as to remove all solid particles, strongly acidulated with acetic acid, and treated with a few cubic centimeters of a saturated solution of sodium tungstate also strongly acidulated with acetic acid. In case the fluid is

¹ Vrtljschr. f. gerichtl. Med., 1901, 21, 227.

deeply colored with blood-pigment, 5 or 10 c.c. of the tungstate solution may be necessary. If there be much blood-pigment present in the fluid, the addition of the sodium tungstate solution will produce a distinct, light-colored precipitate, which will be quite bulky, but which, on boiling the fluid in the flask or test-tube, will become aggregated in the form of dense, chocolate-colored flocculi. These can be collected on a filter-paper, washed with water, dried, and tested by the hemin test; or, spectroscopically, by dissolving a part of it in very dilute sodium or ammonium hydroxid, when the spectrum of hematin in alkaline solution may be seen.

If there be not a sufficient amount of blood-pigment to impart any perceptible color to the extract obtained by washing, the addition of the sodium-tungstate solution will cause perhaps only a very slight turbidity. In this case the mixture should be actively boiled and set aside for a day or two to settle completely. The tungstate precipitate of the blood-pigment will be found in the light sediment at the bottom. The supernatant clear fluid should then be decanted from the sediment, and the latter transferred to a watch-glass, in which it can be washed by collecting it in the center of the watch-glass by gently rotating the latter, and the supernatant fluid removed by carefully introducing strips of blotting- or filter-paper. In this way, by careful manipulation, the precipitate can finally be collected in only a drop or two of water, which can be transferred to a glass slide, evaporated by gentle heat, and the hemin test applied.

A number of oxidation reactions have been applied to blood-stains, guaiacum, benzidin, phenolphthalin, and fluorescein, giving the best results.

The Guaiacum Test.—This test depends on the principle that, if a solution of blood-pigment be treated with a few drops of very dilute tincture of guaiacum and then with a drop or two of a solution of hydrogen dioxid, a blue color is immediately produced. This test is also called Van Deen's test. Van Deen, however, used ozonized oil of turpentine instead of the hydrogen dioxid solution, but the latter is preferable, since it is cleaner and can always be obtained.

A minute fragment of the stain, or a few fibers of the stained fabric, should be placed in a small porcelain evaporating dish or crucible, treated with a drop of water in order to dissolve a portion of the pigment, and then a few drops of the guaiacum tincture added; if no blue color result, it shows that no substance is present that will produce the blue color with the guaiacum alone; then a drop or two of the solution of hydrogen dioxid should be added, when, if there is the slightest trace of blood-pigment present, a bright blue color will be produced immediately.

This test is an extremely delicate one, and will, according to Wormley, react with blood-pigment in a solution of only 1 part in 5000. It will also react with old stains as well as with fresh ones; if the stain be very old, however, it is necessary to soak it a longer time in water. A piece of moistened filter-paper pressed for a moment on a blood-stain will generally remove enough of the coloring-matter to give this

reaction; in this case the tincture of guaiacum and the hydrogen dioxid may be applied directly to the paper. This is a valuable and practical preliminary test. A suspected spot may be covered with a piece of moistened filter-paper and the latter pressed on the spot for a moment, the paper removed, and the spot on the paper tested. If no blue color be produced on the paper, we may be positive that the stain is not a blood-stain; if, however, a blue color is produced, it is an indication that the stain may contain blood, the presence of which must be confirmed by other tests or methods of examination. The tincture of guaiacum used in this test must be freshly prepared, and must be made from perfectly clear pieces of the resin, which should be obtained from the center of a freshly broken clear lump.

Schaer¹ has modified the test as follows: The fragment of the blood-stain, especially if it is an old stain, is moistened with very dilute acetic acid for a few minutes and then treated with a solution containing 1 per cent. of guaiacum and from 70 to 75 per cent. of chloral hydrate. Then, if no blue color appears, there is added a drop or two of the following solution of hydrogen dioxid: 15 c.c. of a 3 to 5 per cent. solution of hydrogen dioxid free from acid, with 25 c.c. alcohol, 5 c.c. chloroform, and 1½ c.c. glacial acetic acid. The blue color will appear immediately if blood-pigment is present in the stain.

There are many other substances than blood-pigment that will produce a blue color with the guaiacum test. The following have been shown by different observers to be capable of producing this same reaction: Potato skin, casein, glue, many compounds of iron, particularly the chlorid, acetate, and citrate, and, to a slight degree, ferric hydroxid, which is always present in iron-rust; according to Huenefeld,² ferric sulphate, iron alum, cupric sulphate and nitrate, the double chlorid of gold and sodium, manganese dioxid, potassium permanganate, and, according to Wesener, indigo, so that the test is not reliable in the case of stains on cloth that has been dyed with indigo.

Practically, therefore, the negative result obtained by this test is of greater value than the positive result, since it shows that the stain in question does not contain blood-pigment in such a form as to be soluble in the ordinary solvents.

Phenolphthalin Test.—Phenolphthalin is a more delicate and useful reagent than guaiacum. With phenolphthalin Delearde and Benoit³ were able to detect blood at a dilution of 1 part in 1,000,000 and Kastle⁴ recognized blood at a dilution of 1 part in 80,000,000.

In order to prepare the phenolphthalin, phenolphthalein is dissolved in a considerable excess of 30 per cent. sodium hydroxid solution and boiled with an excess of zinc dust until a few drops of the strongly alkaline liquid no longer give the color of phenolphthalein after neutralization with hydrochloric acid and the addition of sufficient alkali

¹ Jour. Pharm., 1899, 361-370.

² Die Blutproben vor Gericht.

³ Compt. rend. Soc. de biol., 1908, 64, 990.

⁴ Bull. 51, Hyg. Laboratory, 1909.

to give a slightly alkaline reaction. The solution is then decanted from the excess of zinc dust and the phenolphthalin is precipitated by acidifying with hydrochloric acid. The substance is then collected on a filter and purified by several crystallizations from water and alcohol in the following manner: The phenolphthalin is dissolved in the smallest quantity of boiling alcohol in which it will dissolve, filtered if necessary, and cold water gradually added with constant stirring until the compound is precipitated out as a white crystalline precipitate. From three to five crystallizations are carried out in precisely this manner, and in this way phenolphthalin is finally obtained in the form of a white crystalline compound entirely free from all traces of phenolphthalein.

One of the great advantages of phenolphthalin in work of this kind is that we know we are dealing with a perfectly definite compound, the purity of which can be determined simply and easily whenever desired, and which on oxidation passes into another equally definite compound, the smallest amount of which can be readily detected by means of alkali, and which may be determined very accurately by colorimetric methods.

Alkaline Phenolphthalin.—This reagent is prepared by dissolving 0.032 gram of phenolphthalin in 21 c.c. of N/10 sodium hydroxid and adding sufficient water to make the volume of the solution to 100 c.c. This reagent may also be prepared by bringing together 1 c.c. of N/10 sodium hydroxid with somewhat more phenolphthalin than will dissolve in this quantity of alkali, diluting with 10 to 20 c.c. of water, filtering, and adding to the filtrate 20 c.c. of N/10 sodium hydroxid and sufficient water to make up to 100 c.c. Since phenolphthalin itself is practically insoluble in water and since 1 c.c. of N/10 sodium hydroxid exactly neutralizes 0.032 gram of the compound, we obtain a solution by the latter mode of procedure of the same concentration as that prepared by the first method, no weighing being required (Kastle).

When first prepared, the alkaline solution of phenolphthalin is perfectly colorless. On long standing, however, it gradually acquires a faint color, due to the oxidation of traces of the compound by atmospheric air. To 1 c.c. of the alkaline phenolphthalin reagent add 0.5 c.c. of the extract and 1 drop of 3 per cent. hydrogen peroxid. In five minutes a deep purplish-red or pink color will be obtained in the presence of blood. The control test is made by mixing 0.5 c.c. of distilled water, 1 c.c. of the reagent, and a drop of peroxid; if the reagent has been properly prepared only a trace of pink will be found. Kastle reports that animal tissues in many cases retard the oxidation of phenolphthalin under the influence of blood. If a positive test is obtained, care should be taken, in this as in the other oxidation tests, to exclude oxidases or peroxidases by boiling, and the salts of heavy metals and other oxidizing agents by chemical methods.

Benzidin Test.—This is also a very delicate test for blood. To a saturated solution of benzidin in alcohol or glacial acetic acid freshly prepared, or to a small amount of benzidin about the size of a grain of

rice placed on a white tile with a few drops of glacial acetic acid, add an equal volume of 3 per cent. hydrogen peroxid and $\frac{1}{2}$ c.c. of the solution under examination. Make a control test substituting water for the unknown solution. A greenish-blue color is obtained in the presence of blood. The benzidin reaction serves to detect blood when present in a dilution of 1 part in 300,000.

The fluorescence of hemoglobin derivatives, especially hematoporphyrin is recommended as a sensitive test for blood-pigment.

Fuld finds rhodamine B extra very sensitive as a reagent: Take 0.2 gram of the dye in 50 c.c. alcohol, add 5 grams zinc dust and 4 c.c. 10 per cent. NaOH to the boiling alcohol; on the addition of 3 per cent. hydrogen peroxid, this gives a red color with blood in a dilution of 1 part in 10,000,000.

The Protein Test.—This test is of comparatively little value, since there are so many other substances besides blood that contain protein. It depends on the fact that, if a solution of protein, such as must be contained in a solution of blood or of a blood-stain, be heated to near the boiling-point of water (after faint acidulation if alkaline or neutral), the protein is coagulated. If the solution contain at the same time blood-pigment, this latter will be carried down with the coagulated protein, and will impart to it a more or less brownish tint. Practically, in the testing of blood-stains, this test is obtained during the first part of the hemin test. In evaporating the drop of the solution of the blood-stain on the glass slide, when the temperature reaches approximately 75° or 80° C. (167° or 176° F.), the drop may be seen to become turbid. This is due to the coagulation of the protein, there usually being in an ordinary blood-stain a sufficient quantity of protein in the solution. This reaction alone does not serve to distinguish between a stain containing blood and one containing any other albuminous fluid.

Spectroscopic Test for Blood.—The spectroscopic test for blood-pigment depends on the fact that, when a solution of hemoglobin, its compounds, or decomposition products is placed in front of the slit of a spectroscope, certain rays of light will be absorbed, thus producing dark bands called absorption bands in certain portions of the solar spectrum. The position of these bands varies with solutions of the different blood-pigments, since these different pigments absorb different rays of light. The discovery of the absorption bands of oxyhemoglobin by Hoppe-Seyler in 1862 gave an impetus to this method of examination, resulting later in the discovery of the peculiar bands formed by solutions of the other compounds of hemoglobin and its colored decomposition products.

When a sufficient amount of blood can be obtained for examination, whether in the fresh state or in the form of a dried stain, as in the case of the drying of a small pool of blood, a sufficient quantity of solution of blood-pigment may easily be made to permit of its examination with the ordinary large laboratory spectroscopes; the position of the absorption bands may be located by means of the scale with which the better instruments are provided. It frequently happens, however, that the

amount of material at hand in medicolegal cases is not sufficient to yield the required quantity of solution. In such cases resort must be had to one of the smaller spectroscopes, and in some cases to the so-called microspectroscope, which is, more properly speaking, a spectroscopic eye-piece applied to the tube of a microscope. Of the smaller spectroscopes, the most convenient is the Vogel's direct-vision pocket-spectroscope, which can be mounted on a block. It is provided with a prism and reflector so arranged that two spectra may be obtained—one of the light that passes through the solution of the suspected stain, and the other either the ordinary solar spectrum or a spectrum caused by light passing through a solution of some known blood-pigment for the purpose of comparison. This direct-vision spectroscope requires but an extremely small amount of solution, which may be contained in small $\frac{1}{2}$ -dram phials set into holes bored in the block at the proper points. These points are so chosen that the light passing through the center of the fluid will pass directly into the slit of the spectroscope, or will be reflected into it by the mirror and prism. In looking through the instrument thus arranged the two spectra will be seen, one just above the other.

In most instances the blood-stains are so small that the spectroscopic eye-piece must be used in a microscope. The instrument usually used is the spectroscopic eye-piece of Sorby or Abbé. For the description of these instruments the reader is referred to works on optical apparatus or to the catalog of the manufacturers of microscopes and microscopic accessories.

Oxyhemoglobin.—The characteristic spectrum of oxyhemoglobin can be seen only in very dilute solution. If a solution containing about 0.75 per cent. be examined in a layer 1 cm. (0.4 inch) thick, most of the rays of light will be absorbed between the lines *D* and *b*, thus forming a single large absorption band. On diluting the solution still further, this large absorption band resolves itself into two bands that are very distinct: one, the darker and more distinct but narrower of the two, is called α , and lies very near the line *D*, while the wider but less distinct band, called β , lies near the line *E*. The first four spectra in Fig. 81 show the appearance of the bands produced by solutions of oxyhemoglobin in different degrees of concentration. These four spectra are taken from Preyer's plates,¹ with the addition of the wave-length scale by Gamgee (see also Plate 6, No. 2).

Hemoglobin.—As mentioned, the oxygen contained in oxyhemoglobin is loosely combined, so that it can be removed from the oxyhemoglobin easily by either mechanical means or chemical agents. It may be exhausted by a vacuum-pump or removed by the action of reducing agents, such as a dilute solution of ammonium sulphid, or a solution of ferrous sulphate to which a small quantity of citric or tartaric acid has been added, and then just enough ammonia to render it faintly alkaline (Stokes' reagent). From this treatment there results a solution of hemoglobin that has a darker color than that of oxyhemoglobin.

¹ Die Blut-Krystalle, Jena, 1871.

If this solution be examined with a spectroscope, a single absorption band, called γ , is seen occupying the space between the positions formerly occupied by the oxyhemoglobin bands, α and β . It is gener-

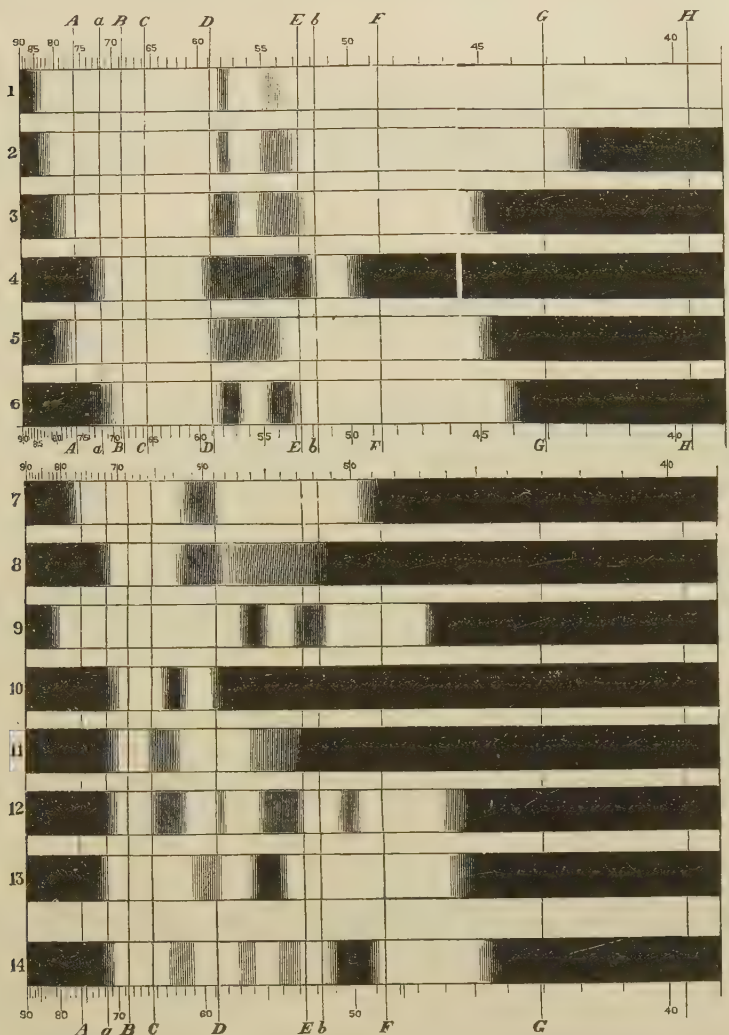


FIG. 81.—Spectra: 1, 2, 3, 4, Oxyhemoglobin of various degrees of concentration; 5, hemoglobin; 6, CO-hemoglobin; 7, 8, hematin in alkaline solution, dilute and concentrated; 9, hemochromogen (Stokes' reduced hematin); 10, methemoglobin; 11, acid hematin (blood treated with acetic acid); 12, acid hematin in alcoholic solution; 13, acid hematoporphyrin; 14, alkaline hematoporphyrin.

ally less sharply defined than the oxyhemoglobin bands (see spectrum 5; also Plate 6, No. 3).

Methemoglobin.—This, as mentioned, is also a compound of hemoglobin and oxygen, but a much more stable one, the oxygen conse-

quently being removed from it with much greater difficulty. It is sometimes formed from hemoglobin in the living body, as in cases of hemoglobinuria and of potassium chlorate poisoning. Putrefaction also changes some of the hemoglobin-into methemoglobin. An old blood-stain that has been exposed to direct sunlight contains some methemoglobin.

A solution of methemoglobin examined with the spectroscope shows a dark absorption band in the red between *C* and *D*, lying a little nearer to *C* than to *D* (see spectrum 10; also Plate 6, No. 4). If properly diluted, two faint bands may be seen between *D* and *E*, in a position similar to the oxyhemoglobin bands; and still a fourth band has been described in the blue, between *b* and *H*.

Carbon Monoxid Hemoglobin.—This stable compound is formed by the action of carbon monoxid (CO) on hemoglobin or oxyhemoglobin. It is of medicolegal importance in cases of poisoning by carbon monoxid, which results from the inhalation of illuminating gas containing it, such as water-gas, or from the inhalation of the fumes from burning charcoal.¹ Solutions of this compound have a bright cherry-red color, which is seen in the blood and tissues of those poisoned with CO. This peculiar color can be preserved in such cases by adding to the blood an equal volume of a concentrated solution of borax. Solutions of carbon-monoxid hemoglobin give a spectrum similar to that of oxyhemoglobin, except that the two bands lie a little nearer the violet end of the spectrum. It can be distinguished from the oxyhemoglobin spectrum, however, by the fact that it remains unchanged on heating the specimen under examination with ammonium sulphid (see spectrum 6, and Plate 6, No. 7).

Hematin.—The recognition of this pigment is of importance in those cases in which the stain has been subjected to the action of those agencies that cause decomposition of the hemoglobin. In order to extract the hematin from a blood-stain so as to prepare it for spectroscopic examination it is necessary to treat the stain, or a portion of it, with a dilute alkali (sodium or ammonium hydroxid), with glacial acetic acid, or with alcoholic solution of sulphuric acid, since hematin is insoluble in water, alcohol, and ether.

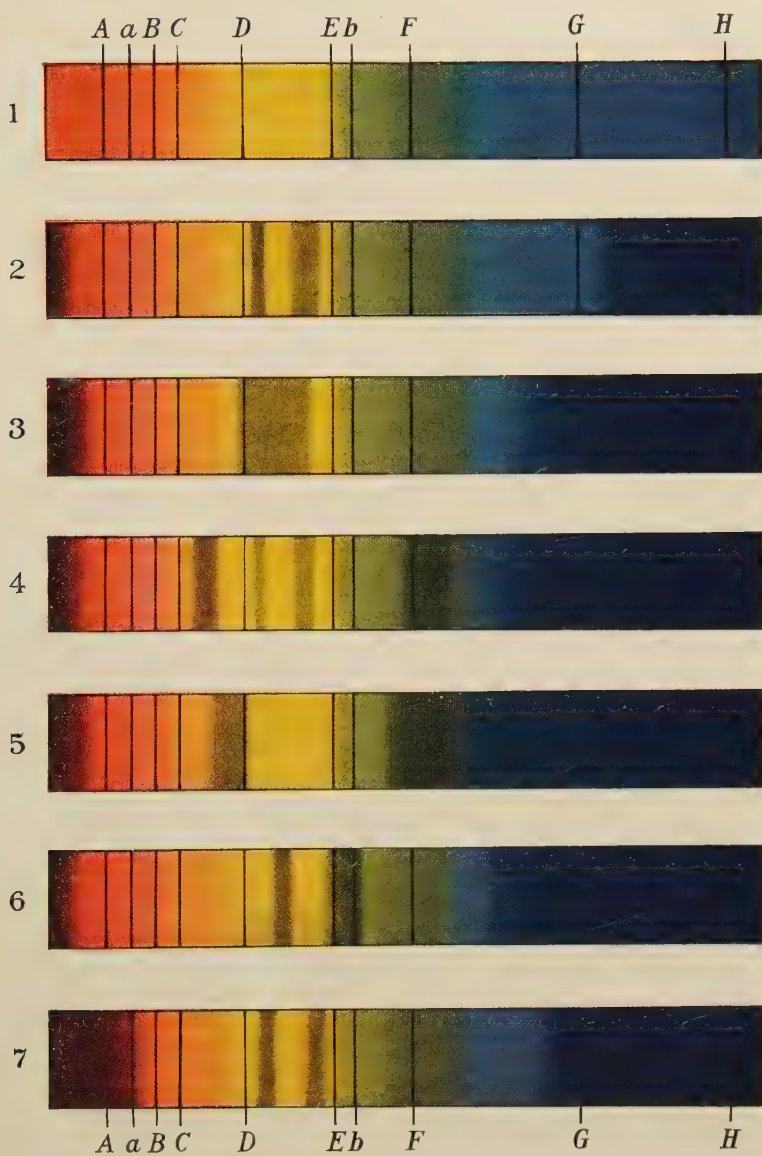
The acid and the alkaline solutions of hematin give different spectra. The spectrum of hematin in alkaline solution has a dark band between *C* and *D*, lying near *D*, and if sufficiently concentrated, overlapping *D*, while the violet end of the spectrum will be almost absorbed (see spectra 7 and 8, and Plate 6, No. 5). The spectrum of hematin in acid solution has an absorption band between *C* and *D*, very close to the line *C* (see spectrum 11). In an alcoholic sulphuric acid solution properly diluted the spectrum may have four bands, one between *C* and *D*, nearer *C*; a very faint band, not always visible, just to the right of *D*; a broad band between *D* and *E*, nearer *E*; and the fourth band between *b* and *F*, a little nearer *b* (spectrum 12).

Hemochromogen or Reduced Hematin.—This is produced by

¹ See chapter on Gaseous Poisons.

PLATE 6.

BLOOD SPECTRA



1. Solar spectrum.
2. Oxyhemoglobin.
3. Hemoglobin.

4. Methemoglobin in dilute solution.
5. Hematin in alkaline solution.
6. Hemochromogen, or reduced hematin.
7. Carbon-monoxid hemoglobin.

treating an alkaline solution of hematin with a reducing agent, such as ammonium sulphid or Stokes' reagent. Its solutions give a well-defined absorption band midway between *D* and *E*, and a fainter band between *b* and *E* (see spectrum 9, and Plate 6, No. 6). On exposure to the air an alkaline solution of hemochromogen absorbs oxygen and is reconverted into hematin.

Hematoporphyrin.—This is formed by dissolving blood-pigment in concentrated sulphuric acid or by heating it with concentrated hydrochloric acid. The solution in concentrated sulphuric acid gives a spectrum having two bands, one faint and to the left of *D*, and the other more distinct, between *D* and *E* (see spectrum 13). In dilute alkaline solution its spectrum has four bands, one faint and midway between *C* and *D*, the second and third rather faint, and having a position similar to the α and β oxyhemoglobin bands; and the fourth, a broad dark band reaching from *b* nearly to *F* (spectrum 14).

Method of Examination.—The method of treating a blood-stain for spectroscopic examination varies according to the quantity of material at disposal and according to the age of the blood-stain—that is, whether the hemoglobin is present in the stain unchanged or has been decomposed by agencies mentioned above. If plenty of material be available and the blood-pigment be mostly undecomposed, a portion of the stain can be treated with a little water or dilute salt solution, and examined directly with the direct-vision spectroscope, and the oxyhemoglobin bands recognized; the solution should then be treated with a little reducing agent and the single band of hemoglobin obtained. If the blood-pigment has become partially decomposed in the stain, the spectrum of methemoglobin may be seen either alone or combined with the oxyhemoglobin spectrum. If so much decomposed that it no longer yields any color to water, it should be treated with a little dilute sodium hydroxid; the resulting solution will give the spectrum of hematin in alkaline solution if the stain contained blood. Ammonium sulphid added to this solution will give the spectrum of hemochromogen. By using glacial acetic acid instead of dilute sodium hydroxid on a stain that is insoluble in water, the spectrum of hematin in acid solution may be seen. If the stain has been heated to a high temperature, so that hematoporphyrin has been formed, a fragment of the stain must be treated with concentrated sulphuric acid, which will dissolve it, giving a purplish-red solution showing the spectrum of hematoporphyrin in acid solution.

If the amount of material be minute, so that it is necessary to use a microspectroscope, the best method of examination to be employed is that recommended by Richardson.

“Procure a glass slide with a circular excavation in the middle, called by dealers a concave center, and moisten it around the edges of the cavity with a small drop of diluted glycerin. Thoroughly clean a thin glass cover about $\frac{1}{8}$ inch larger than the excavation; lay it on white paper, and upon it place the tiniest visible fragment of a freshly dried blood-clot. This fragment will weigh from $\frac{1}{50000}$ to $\frac{1}{25000}$

grain. Then, with a cataract needle, deposit on the center of the cover, near your blood-spot, a drop of glycerin about the size of a small period, and with a dry needle gently brush the blood to the brink of your microscopic pond, so that it may be just moistened by the fluid. Finally, invert your slide upon the thin glass cover in such a manner that the glycerined edges of the cavity in the former may adhere to the margins of the latter, and, turning the slide face upward, transfer it to the stage of the microscope. By this method it is obvious that we obtain an extremely minute quantity of strong solution of hemoglobin whose point of greatest density, generally in the center of the clot, is readily found under a $\frac{1}{4}$ -inch objective, and tested by the adjustment of the spectroscopic eye-piece. After a little practice it will be found quite possible to modify the bands by the addition of sulphuret of sodium solution, as advised by Preyer.

"In cases of this kind, where the greatest possible economy, or even parsimony, of the material is needful, I would advise the following mode of procedure for proving and corroborating your proof of the existence of blood, so that its presence in a stain may be affirmed with *absolute certainty*.

"From a suspected blood-spot upon metal, wood, paper, muslin, or cloth scrape with a fine, sharp knife two or three or more minute particles of the reddish substance, causing them to fall near the middle of a large, thin glass cover. Apply in close proximity to them a very small drop of $\frac{3}{4}$ per cent. salt solution, bring the particles of supposed blood-clot to its edge, and proceed as I have already directed.

"After thus examining the spectrum of the substance you may generally, by rotating the stage, cause the colored fluid to partly drain away from the solid portion, wherein, under favorable circumstances, should the specimen be blood, the granular white blood-globules become plainly visible, as do also cell walls of the red discs. Among the latter, if your mental and physical vision be keen enough, you can, by the aid of a $\frac{1}{25}$ immersion lens and an eye-piece micrometer, measure a series of corpuseles accurately enough to discriminate human blood from that of an ox, pig, horse, or sheep,"

Since there are a few substances, solutions of which give a spectrum somewhat resembling that of oxyhemoglobin, such as solutions of alkanet root in alum and those of cochineal, the spectroscopic examination should not be restricted to the recognition of the spectrum of oxyhemoglobin alone. The stain should be treated with the different reagents, so as to obtain several of the blood spectra. The solution of oxyhemoglobin should, after the oxyhemoglobin bands have been recognized, always be converted into hemoglobin and again examined, since the vegetable solutions mentioned above are not changed by the action of reducing agents.

The methods of examination heretofore described enable us to determine simply the presence of the coloring-matter of blood, which throws no light whatever upon the kind of blood, since the red coloring-matter

—hemoglobin—is contained in the blood of all vertebrates except the *amphioxus* and *leptocephalus*,¹ and in that of many of the invertebrates.

In order to obtain any information as to the nature of the animal from which the blood in question originated, resort must be had to the microscopic investigation, for the purpose of determining, if possible, the form and size of the red blood-cells, and to the precipitin or biologic test.

Microscopic Examination of Blood.—The red blood-cells differ in different animals. In birds, reptiles, and fishes the red corpuscle is oval in shape and has a distinct nucleus, while in most mammals it is a circular, biconcave disc without a nucleus; in the camel and llama tribe, however, the red cells are oval in shape, but have no nucleus. The distinction between any kind of blood having nucleated red cells and one having non-nucleated red cells offers no difficulty whatever, even in the case of dried stains, since the nuclei are very stable and not readily destroyed, and can be very easily recognized by their high density. The microscopic distinction between the different kinds of mammalian blood presents much greater difficulty, since, with the exception of the camel tribe, the only difference is in the size of the red blood-cells. This difference in size lies within such narrow limits that in some cases the positive distinction, by the microscope, between the blood of certain different animals is absolutely impossible, particularly after the blood has been dried. In other cases, however, the difference in size is so marked that there is no difficulty in distinguishing between them if the red cells have not been decomposed. This distinction is made by measuring the diameter of a large number of red cells and thus determining the average size. This requires the use of the highest powers of the microscope and the most delicate and accurate scales for measuring.

In the microscopic examination of blood-stains the expert is not required to state with certainty from what animal the blood originated in any given case. He is only required to make a complete scientific investigation of the stains in question, to state the facts as he finds them, and with what those facts are consistent. He must state whether or not a stain contains blood, and, if blood be present and he has been able to obtain the red blood-cells for microscopic investigation, whether or not these red blood-cells are nucleated or non-nucleated; if non-nucleated, what is the average size of the red blood-cells found. Only perfect red blood-cells must be measured. In some cases it is alleged by the accused that the blood-stains were caused by slaughtering or dressing a bird or a fish, or some animal, like a pig, ox, or sheep. In such cases it is obviously only necessary for the expert to state whether or not the red blood-cells that he found in the stain were or were not consistent with the explanation advanced. If the red cells that he found were non-nucleated circular discs, the blood forming that stain could not have emanated from a bird, fish, or reptile. If he finds that the average diameter of the red blood-cells is greater

¹ Lankester, Proc. Royal Soc., 1872, 21, 71.

than $\frac{1}{3500}$ inch, the blood in that stain could not have emanated from any animal whose red blood-cells are smaller than $\frac{1}{4000}$ inch, and, therefore, could not have come from a pig, ox, horse, sheep, or goat.

As to the structure of the red blood-cells, authorities differ. Many of the older physiologists considered that the blood-cells had a distinct cell-wall containing a fluid colored with the red pigment, while others thought that they consisted of a stroma or network that is colorless, elastic, and made up of a protein substance the interstices of which contain the coloring-matter. This latter theory appears to be supported by the weight of evidence.

When the red blood-cells of mammalian blood are treated with water or with any fluid the density of which is less than that of the blood-serum, they undergo a distinct change in form, owing to the absorption of water and the loss of their own contents by osmosis. They first lose their biconcavity, then become biconvex, and finally spheric. While this change is taking place the distance between the two edges diminishes, so that finally the diameter of the cell, which has become spheric, is only about two-thirds of the original diameter when the cell had its normal biconcave shape. At the same time its density has disappeared, so that it is much more difficult to see, the outline of the cell being a mere line. Finally, if this influence continues, the cells become entirely destroyed.

A similar change in the form and size of many of the red blood-cells takes place when the blood dries slowly, so that, in preparing a blood-stain for microscopic examination, that portion of the stain should be selected that has dried most quickly, since there it would be expected to find a larger proportion of cells that have preserved their normal shape and size than in the center of the clot, where the drying has taken place more slowly.

When blood is treated with saline solutions of greater density than blood-serum, the red cells become shrunken or shriveled and the edges irregular, or what is termed "crenated," but they do not lose their density and color. The red blood-cells are generally destroyed by acids and alkalis. Thus, while there are many agencies that may cause a diminution in the size of the red blood-cells, as yet none is known outside the living body that will cause an increase in their size or diameter. The influence of disease upon the size and form of the red blood-cells will be referred to later.

The size of the red blood-cells differs considerably in different animals, and to a certain extent within narrow limits in the same animal. As a rule, in animals having nucleated red blood-cells, the cells are much larger than in those having non-nucleated cells, as, for instance, in one of the Louisiana reptiles (*Amphiuma*), the red cell is about $\frac{1}{350}$ inch in its long diameter, large enough to be seen by the unaided eye. Of the mammals, as will be seen by the table, the elephant has the largest red blood-cells, the average size being $\frac{1}{2745}$ inch. In medico-legal cases generally the question only arises as to the distinction between

the blood of man and that of the domestic animals in the case of mammalian blood-stains. In these the red blood-cells vary in their average diameter from about $\frac{1}{6000}$ to $\frac{1}{3000}$ inch. As will be seen from the table, the authorities differ but slightly with reference to the average diameter of the human red blood-cell. All agree that it is between $\frac{1}{3300}$ and $\frac{1}{3200}$ inch. Gulliver and Formad place the average at $\frac{1}{3200}$ inch; Wormley at $\frac{1}{3250}$ inch; the French Committee appointed by the Medicolegal Society of France in 1873, at $\frac{1}{3257}$ inch; Masson gives the same diameter, and Carl Schmidt, at $\frac{1}{3300}$ inch. Formad states, as the result of a large series of measurements, that 90 per cent. of the red blood-cells will measure between $\frac{1}{3300}$ and $\frac{1}{3100}$ inch, only 10 per cent., therefore, falling outside of these limits, which he considers the normal. The smallest red blood-cell is $\frac{1}{3800}$ and the largest $\frac{1}{2900}$ inch. Hayem¹ states that in every 100 red blood-cells about 12 will be larger than the average and about 12 smaller than the average.

FIG. 82.—Human ($\times 2500$).FIG. 83.—Dog ($\times 2500$).

The dog, pig, horse, ox, cow, cat, sheep, and goat are the only domestic mammals whose blood is liable to be of importance in medico-legal cases with reference to its distinction from human blood. Of these, the blood of the dog approaches most nearly in size to human blood. Figures 82 and 83 show the red cells of man and dog respectively, magnified 2500 diameters. The average diameter of the red blood-cell in dog's blood is about $\frac{1}{3550}$ inch, while that of all the other animals mentioned is less than $\frac{1}{4000}$ inch; the red cells of the ox, pig, horse, and cat vary from $\frac{1}{4400}$ to $\frac{1}{4200}$ inch; the red blood-cell of the sheep is about $\frac{1}{5000}$, and that of the goat still smaller—less than $\frac{1}{6000}$ inch. The size of the goat's blood-cell is, therefore, approximately one-half that of the human.

The following table gives the average measurements as reported by various hematologists. The older authorities, Gulliver and Carl

¹ Du Sang, Paris, 1889.

AVERAGE SIZE OF THE RED BLOOD-CELLS

MAMMALS.	Gulliver.	Wormley.	Formad.	Richardson.	C. Schmidt, 1898.	French Med- icolegal So- ciety, 1873.	Masson, 1885.	Dragendorff.	Woodward.
Man	1-3200	1-3250	1-3200	1-3224	1-3330	1-3257	1-3256	1-3300	1-3092
Monkey	1-3412	1-3382		1-3395					
Opossum	1-3557	1-3145							
Guinea-pig	1-3538	1-3223	1-3400				1 3300		1-3213
Kangaroo	1-3440	1-3410							
Musk-rat	1-3550	1-3282							
Dog	1-3532	1-3561	1-3580	1-3542	1-3630	1-3479	1-3577	1-3628	1 3246
Rabbit	1-3607	1-3653	1-3662		1-3968	1-3681	1-3628	1-3968	
Rat	1-3754	1-3652			1-3968				
Mouse	1-3814	1-3743			1-4166				
Pig	1-4230	1-4268	1-4250	1-4230	1-4098	1-4233	1-4098	1-4098	
Ox	1-4267	1-4219	1-4200	1-4267	1-4385	1-4535	1-4233	1-4385	
Horse	1-4600	1-4243	1-4310		1-4456	1-4535			
Cat	1-4404	1-4372			1-4535	1-3907	1-4456	1-4535	
Elk	1-3938	1-4384							
Buffalo	1-4586	1-4351							
Wolf (prairie)	1-3600	1-3422	1-3450						
Bear (black)	1-3693	1-3656							
Hyena	1-3735	1-3644							
Squirrel (red)	1-4000	1-4140							
Raccoon	1-3950	1-4084							
Elephant	1-2745	1-2738							
Leopard	1-4319	1-4390							
Hippopotamus	1-3422	1-3560							
Rhinoceros	1-3765	1-3649							
Whale	1-3099			1-3090					
Tapir	1-4000	1-4175							
Lion	1-4322	1-4143							
Ocelot	1-4220	1-3885							
Mule		1-3760							
Ass	1-4000	1-3620							
Ground-squirrel		1-4200							
Bat	1-4175	1-3966							
Sheep	1-5300	1-4912	1-5000	1-5300	1-5649	1-5080		1-5649	

Schmidt, obtained their results with low magnifying powers of the microscope, and agree astonishingly with the results obtained by others using higher powers and much better instruments. The figures given are in vulgar fractions of an inch, which is the scale almost universally used in this country, and which it is necessary to use in court, since the average jurymen knows nothing about the metric scale. Where the original measurements were given in thousandths of a millimeter they have been reduced to vulgar fractions of an inch.¹ The first two columns of the table are taken from the appendix to the second edition of Wormley's *Micro-Chemistry of Poisons*, p. 733 *et seq.*

Method of Examination.—In determining the size of the normal red blood-cells of man and different animals two methods have been adopted: One consists in preparing a thin layer of fresh blood and measuring the red cells while still suspended in the serum, and the other in preparing a very thin layer of dried blood and measuring those cells that have retained their normal form.

In making a layer of fresh blood sufficiently thin for this purpose care must be taken that the slides and cover-glasses are perfectly

¹ A thousandth of a millimeter is equal to 0.00003937 inch. It is often called a micromillimeter, or micron, and is represented by the Greek letter μ . These terms are frequently used in connection with the measurement of microscopic objects.

AVERAGE SIZE OF THE RED BLOOD-CELLS (*Continued*)

MAMMALS.	Gulliver.	Wormley.	Formad.	REPTILES.	Gulliver.	Wormley.
Ibex.....		1-6445		Tortoise(land) {Long diameter	1-1252	1-1250
Goat.....	1- 6366	1 6189	1-6100	{Short "	1-2216	1-2200
Sloth.....	1- 2865			Turtle (green) {Long "	1-1231	
Platypus (duck-billed).....	1- 3000			{Short "	1-1882	
Capybara.....	1- 3190	1-3164		Boa {Long "	1-1440	1-1245
Seal.....	1- 3281			{Short "	1-2400	1-2538
Woodchuck.....	1- 3484			{Long "	1-1274	
Musk-deer.....	1-12325			Viper..... {Short "	1-1800	
Beaver.....	1- 3325			{Long "	1-1555	
Porcupine.....	1- 3369			Lizard..... {Short "	1-2743	
Llama..... {Long diameter	1- 3361	1-3201				
{Short "	1- 6229	1-6408		BATRACHIANS.		
Camel..... {Long "	1- 3123	1-3331		Frog..... {Long diameter	1-1108	1-1089
{Short "	1- 5876	1-5280		{Short "	1-1821	1-1801
				Toad..... {Long "	1-1043	
BIRDS.				{Short "	1-2000	
Chicken... {Long diameter	1- 2102	1-2080		Triton..... {Long "	1-848	
{Short "	1- 3436	1-3483		{Short "	1-1280	
Turkey... {Long "	1- 2045	1-1894		Proteus..... {Long "	1-400	
{Short "	1- 3598	1-3444		{Short "	1-727	1-358
Duck..... {Long "	1- 1937	1-1955		Amphiuma {Long "	1-363	1-622
{Short "	1- 3424	1-3504		{Short "	1-615	
Pigeon... {Long "	1- 1973	1-1892				
{Short "	1- 3643	1-3804		FISHES.		
Goose..... {Long "	1- 1836			Trout..... {Long diameter	1-1524	
{Short "	1- 3839			{Short "	1-2460	
Quail..... {Long "	1- 2347			Perch..... {Long "	1-2099	
{Short "	1- 3470			{Short "	1-2824	
Dove..... {Long "	1- 2005			Pike..... {Long "	1-2000	
{Short "	1- 3369			{Short "	1-3555	
Sparrow... {Long "	1- 2140			Eel..... {Long "	1-1745	
{Short "	1- 3500			{Short "	1-2842	
Owl..... {Long "	1- 1763			Lamprey (Circular).....	1-2134	
{Short "	1- 4076			Lamprey (Diam. of Nucleus).....	1-6400	

clean and free from grease or dust. A very small drop of blood is then placed on the slide by touching the slide to the drop as it issues from a wound made by pricking the lobe of the ear or the tip of the finger with a sharp needle or lancet. The drop on the slide should be immediately covered with a perfectly clean cover-glass, when the blood will spread out under the cover-glass, if the drop has not been too large, in so thin a layer that most of the red blood-cells will be seen lying on their flat surface and not arranged in rouleaux, as would be the case if the size of the drop were too large or the glasses not perfectly clean. If the specimen is found on examination with a low power to be a satisfactory one, the edge of the cover-glass should be surrounded with a thin layer of oil or cement of some kind, so as to prevent evaporation. It may then be examined and the diameter of those red cells which have not been distorted measured.

Most observers have found, however, that it is more convenient to use the dried preparation than the fresh. The red blood-cells are very slightly flattened by the mechanical process adopted in making a very thin layer, but this flattening is of no practical importance, since the diameter of the red cells is so slightly increased that the increase is not perceptible, even with the highest powers. A larger number of the blood-cells are distorted in making a thin dried layer than in making

the fresh preparation, and only the perfectly round cells in mammalian blood should be selected for measurement.

Very thin layers of dried blood may be made by placing a small drop of fresh blood on the edge of a ground-glass slide, and drawing that edge quickly over the surface of another slide, or over the surface of a clean cover-glass. When the layer is sufficiently thin, it will dry almost immediately. This thin layer, if prepared on a slide, may be covered with a cover-glass, which can be fixed on the slide with paraffin, and the red blood-cells, which are of normal shape, may be measured directly. If the preparation has been made on a cover-glass, the cover-glass may be inverted on a glass slide, fixed in the same way, and the normal red cells measured; or the red blood-cells on the slide or cover may be fixed and rendered insoluble by heating the preparation to 120° C. (248° F.). The specimen may then be mounted in Canada balsam and the red cells measured at some convenient time. Or, if desired, the thin layer, after being heated, may be stained with fuchsin or eosin, washed with water, dried, and mounted in balsam. The staining of the red cells makes the edges a little more sharply defined and renders the measuring a little less tiresome.

By the method used in preparing thin layers of blood for clinical examination, a better preparation will be obtained, and one containing a smaller proportion of distorted red cells. This method consists in placing a very small drop of the blood, drawn with the same precautions on an absolutely clean cover-glass, cover with another cover-glass, and, as soon as the blood has spread out, draw the two cover-glasses apart quickly, taking care to keep them in the same plane while drawing them apart. Very satisfactory thin layers of dried blood may thus be obtained. These thin layers may be treated as mentioned in the preceding paragraph, and the normal red blood-cells measured. The white blood-cells are also perfectly preserved in this way.

The method of treating the dried blood-stain for the purpose of bringing out the red blood-cells to their normal shape and of freeing them from extraneous masses so that their edges may be brought plainly into view is very different. A minute fragment of the dried blood-stain must be removed with the point of a knife or a pair of sharp-pointed scissors, transferred to a glass slide, and moistened with some liquid menstruum that will serve to soften and gradually disintegrate the clot, but will not destroy the blood-cells. Various menstrua have been proposed, some preferring alkaline fluids, others acid ones, and others neutral solutions.

Virchow's liquid consists of a 30 or 33 per cent. solution of caustic potash. Roussin recommended a mixture of 3 parts of glycerol, 1 part of sulphuric acid, and water to a specific gravity of 1028. Ranvier's serum was made by dissolving 2 grams of potassium iodid in 100 grams of water, and saturating this solution with iodine. Vibert used a solution of $\frac{1}{2}$ part of corrosive sublimate, 2 parts of common salt, and 100 parts of water. Paccini's fluid was made by dissolving in a mixture of 300 parts of water and 100 of glycerol 2 parts of common salt

and 1 part of corrosive sublimate. Wormley recommended simply a small quantity of distilled water, adding approximately the amount originally present in the dried specimen under examination. If the stain was a very old one, so as to require long soaking in the menstruum, he recommended a dilute solution of glycerol, one having a specific gravity of 1030, and in cases of very old stains, which disintegrate with difficulty, he advised the addition of a little caustic potash to the glycerin or the water. Satisfactory results are obtained from a solution of potassium acetate of a specific gravity of 1030. The addition of a little formalin to this solution improves it by preventing the formation of any fungous growth. Finally a 0.9 per cent. sodium chlorid solution may be used. The cells may be stained in various ways (fuchsin, eosin) to make them seen more easily.

Care must be taken in selecting portions of a dried stain for microscopic examination and measurements to take the dried fragments from some portion of the stain that has dried quickly. If the specimen be taken from the center of a mass of dried blood which has required several hours to dry, the red cells will have taken up a sufficient amount of water to render them spherical, and, therefore, unfit for measurement. The particle of stain thus selected should be moistened with whatever menstruum the observer prefers, covered with a thin cover-glass, and sealed with cement to prevent the evaporation of the fluid. If the blood has dried in a very thin layer on some non-absorbent surface, the thin film may be scraped from the surface with a sharp knife on to a glass slide, and the cells fixed by heating them to 120° C. (248° F.), or by moistening them with a mixture of equal parts of absolute alcohol and ether before treating them with the fluid. The slide should be examined from time to time with a low power, and as soon as cells of the normal form are seen, they may be measured with the high powers. It will be found that the dried blood in some stains disintegrates much more slowly than in others, and, other things being equal, the older the stain, the longer the time required. A stain a few days old disintegrates rapidly, so that measurements may be made as soon as the preparation is completed. Distorted and swollen red cells must not be measured.

More satisfactory results are obtained in cases in which the blood has fallen on a non-absorbent surface. When possible, the examiner should select a dried crust as thin as possible. If the blood has fallen on a piece of linen or cotton cloth in small quantity, so that it has penetrated the fiber of the cloth immediately, as a general rule only unsatisfactory results can be obtained, because the cells adhere tightly to the individual fibers, which, while moist, are somewhat swollen and contract on drying. By this contraction the adherent blood-cells frequently become so distorted as to become unfit for measurement. In such cases a satisfactory result can usually be obtained only when, for some reason or other, complete absorption of the fresh blood has been prevented, as, for instance, if the cloth happened to be more or less starched or if the drop of the fresh blood was a little too large to be completely

absorbed at once. Nucleated blood-cells can, however, readily be seen under these circumstances. The difficulty of discrimination occurs only in the case of mammalian blood-stains.

Blood-corpuscles may be transferred from a stain by placing a solution of celloidin on the suspected spot and allowing it to dry; the resulting pellicle may be removed and examined under a cover-glass under which acetone saturated with eosin is introduced to stain the corpuscles (Dominicis). The best results are obtained with stains on metals, weapons, and stones, and other non-absorbent surfaces. The margins of the blood spots, or thin places, are best suited. Transfer of blood-stains from textile and absorbent materials is more difficult, and a thicker pellicle of celloidin is necessary.

Blood-stains that have been subjected after drying to long-continued action of moisture are generally unsuitable for microscopic measurement, since the red cells absorb a sufficient amount of water to render them abnormal. If the stain has been formed on a non-absorbent surface and has been kept dry, a sufficient number of the red cells will preserve their normal form, so as to be suitable for microscopic measurement, for an indefinite number of years. Blood-stains on iron can be satisfactorily examined only if the iron has been kept completely dry, so that rusting of the iron has not taken place. If, however, the iron has rusted at the point where stained, not only the blood-cells may be totally destroyed, but the blood-pigment may also be decomposed.

Blood-stains are frequently submitted to the expert in which an attempt has been made to wash off the blood with water. Thorough washing will, of course, remove all traces of blood from cloth, but it frequently happens that a hasty attempt to remove the blood-stain, particularly from cloth having a rough surface, will leave a sufficient number of particles of unchanged blood to render a satisfactory examination and measurement possible. If a blood-stain on cotton or linen cloth is treated with water, the blood-pigment is taken up by the water and carried along with it, so that after drying, the whole portion of the cloth that has been wet will show a yellowish stain, but the color will be deeper and browner at the edge than in the center. This is called a diffused or a washed stain, the edges of which, after drying, may be of a deep brown color, while an inch or two from the edge the color is of a much lighter tint. Sea-water removes the blood from a dried stain much more slowly than fresh water.

In the examination of blood-stains great care should be taken to note every peculiarity of each individual stain. As has been mentioned, the form of the stain, together with the distribution of the blood in it, may show from which direction the blood making the stain started. Note should be made as to whether the stain is a spatter or a smooch, or whether it has the appearance of having been wiped or washed. Careful examination should also be made to determine the presence in the stain of any foreign substances, such as hairs, epithelial cells, spermatozoa, pieces of tissue, muscular fibers, or adipose tissue,

bits of bone, etc. It may happen that the presence of such substances will throw light on the nature of the blood making the stain. For instance, any hair found in a blood-stain may resemble that of the victim and be unlike that of the accused, or in case the tissues have been much bruised by a blunt instrument, or perhaps bones fractured and crushed, it is not uncommon to find small particles of tissue, or even a minute fragment of bone, mixed with the blood. Sometimes these foreign substances may be detected by gross inspection; at other times the fragments may be so minute that their presence can be detected only by the microscopic examination.

The following table, taken from Wormley's article, gives the results obtained by him in the examination of dried blood-stains made by different kinds of mammalian blood, the nature of the blood in some instances being unknown to him at the time of the examination:

TABLE OF WORMLEY'S MEASUREMENTS. EXAMINATION OF OLD BLOOD-STAINS

ANIMAL.	Age of stain.	Remarks.	Average.	Fresh blood.
(1) Human.....	2 months old	Stain; unknown.....	1-3358 inch	1-3250 inch
(2) Human.....	2½ "	Stain.....	1-3236 "	1-3250 "
(3) Human.....	3 "	Stain.....	1-3384 "	1-3250 "
(4) Human.....	19 "	Clot.....	1-3290 "	1-3250 "
(5) Elephant.....	13 "	Clot.....	1-2849 "	1-2738 "
(6) Dog.....	4 "	Trace of stain; unknown..	1-3626 "	1-3561 "
(7) Rabbit.....	18 "	Clot.....	1-3683 "	1-3653 "
(8) Ox.....	16 "	Stain.....	1-4544 "	1-4219 "
(9) Ox.....	32 "	Stain; unknown.....	1-4495 "	1-4219 "
(10) Ox.....	4½ years old	Clot.....	1-4535 "	1-4219 "
(11) Buffalo.....	18 months old	Clot.....	1-4312 "	1-4351 "
(12) Goat.....	17 "	Stain.....	1-5897 "	1-6189 "
(13) Ibex.....	18 "	Clot.....	1-6578 "	1-6445 "

Influence of Disease on the Red Blood-cells.—It is well known that in certain diseases the red blood-cells may be altered, both in size and in form, and also the relative proportion between the red and the white blood-cells. Some diseases will diminish their size, as high fever, diphtheria, and septicemia. In pernicious anemia we find some of the red blood-cells of very large size, the diameter being almost double the diameter of the normal red blood-cells. In this disease we may also find many red cells much smaller than normal, even to one-half the normal diameter, called microcytes. Many of the red cells are also distorted (poikilocytes), and some of the red cells in this disease are nucleated. In other forms of anemia we may also find some of these modifications in the form and size of the red blood-cells. In leukemia the number of the red blood-cells in the fresh blood is very greatly reduced, the red cells vary in size and form, and many are nucleated.

There seems to be no record in medicolegal literature of blood-stains from persons suffering from any of these diseases having been submitted to legal investigation. The only error that would be caused by such conditions would be the greater liability of considering the blood to be that of some animal instead of human blood.

OTHER STAINS CONTAINING BLOOD

Diagnosis of these can be made by finding other formed elements mixed with the blood-cells, such as epithelial cells of various kinds, pus, dried mucus, spermatozoa, etc.

Menstrual Stains.—The possibility of determining whether or not a blood-stain was caused by menstrual blood depends largely on the amount of hemorrhage. This, as is well known, differs with different women, and also in the same woman at different times. If the flow be scanty, as at the very beginning or end of the menstrual period, the menstrual blood will have mixed with it a large number of epithelial cells from the vagina. If, however, the flow is abundant, a stain may be made by menstrual blood, particularly a small stain, which does not contain any demonstrable vaginal cells.

The vaginal cells are large polygonal, squamous, epithelial cells, somewhat similar to those from the mucous membrane of the mouth, but having on the average a somewhat larger nucleus. Sometimes we see a vaginal cell with two nuclei. These cells may be exfoliated singly or in small patches containing several layers of cells. If the vagina be inflamed, as in leukorrhea and gonorrhea, these cells will be exfoliated from the membrane in much larger number, and mixed with pus-corpuses. Possibly a cylindric or ciliated cell from the lining membrane of the uterus may be seen mixed with the blood.

If, therefore, we find mixed with the red blood-cells a number of vaginal epithelial cells, we may state that the stain in question is consistent with its having been made by menstrual blood. If, however, we do not find any vaginal cells mixed with the blood, we would not be warranted in concluding that the stain was not made by menstrual blood.

The location of the stains, as on bedding or underclothing, may possibly be of service in deciding the question as to the menstrual origin of the blood-stain in question. In uncleanly women these stains are said to be found more frequently on the back part of an undergarment than on the front.

Nasal Blood-stains.—The detection of nasal blood-stains depends upon precisely the same principle as that of menstrual stains, namely, the finding of various cylindrical and ciliated cells from the mucous membrane of the nose mixed with the blood. If there is but little hemorrhage and the stain be made by forcibly blowing the nose, the blood will be mixed with more or less mucus and cells, and when such a stain becomes dry, it presents a different appearance from an ordinary blood-stain; it is paler and more bulky and, after being moistened, if there is much dried mucus present, it will swell up and have a more or less elastic feel.

If the hemorrhage from the nose has been profuse, a large portion of the blood may not have mixed with it any of the mucous secretion or any of the cells, so that stains may be made from blood coming from the nose, which do not differ in any way from a pure blood-stain. In such cases the location of the stain in question may show whether or not it

could have been made by blood coming from the nose. For instance, in a case in which the accused alleged that the blood on his clothing was due to nose-bleed, a horizontal spatter of blood was found between the folds of a turn-down collar, in such a position that it could not have come from the nose while the collar was around the neck.

As in the case of menstrual stains, therefore, we can only state that a stain in which are found coagulated mucus and cells mixed with the blood is consistent with its having originated from the nose. If we do not find such an admixture, we cannot say that the stain was not caused by nose-bleed unless it is so located that it would be impossible for the blood coming from the nose to have gotten into that position.

THE PRECIPITIN TEST FOR BLOOD

Speaking generally, the only way now known to trace protein substances back to their source, that is, to the species from which they come, is by means of their immune reactions; and in the case of blood and other animal products, practically the only method for purposes of biologic differentiation is the precipitin test. Complement fixation may be used also, but it is more sensitive—almost too sensitive—and more complicated, and in this country this test is not in current use for the identification of blood spots for medicolegal purposes. Because the determination of the ultimate source of blood spots and stains often is vital to the administration of justice, the precipitin test is of special forensic value and interest. The test has been used in this country for the identification of blood for forensic purposes since it was introduced, although probably not so widely as it should or might have been; but it does not appear that any standard method of procedure even with respect to certain essential points as yet has become established, and there are hardly any adequate detailed descriptions of the test.¹ The succeeding statements are taken with minor changes from an article by one of us.²

The precipitin test rests on the fact that when a suitable animal is injected with foreign protein, its serum, when mixed with a solution of

¹ The literature up to about 1908 on precipitins and their medicolegal use is indexed fully in Volume 13 of the Second Series of the Index Catalog of the Library of the Surgeon-General's Office, U. S. Army, Washington, D. C. Reference is made also to Nuttall: Blood Immunity and Blood Relationship, 1904. Graham-Smith and Sanger: The Biological or Precipitin Test for Blood Considered Mainly from Its Medicolegal Aspect, Jour. Hyg., 1903, 3, 258. Graham-Smith: The Biological or Precipitin Test for Blood, Considered Mainly from Its Medicolegal Aspect, II, Ibid., 1903, 3, 354. Sutherland: Blood-stains, Their Detection, and the Determination of Their Source, 1907. Bordet: Studies in Immunity, collected and translated by F. P. Gay, 1909. Uhlenhuth and Steffenhagen: Die biologische Eiweiss-Differenzierung mittels der Präzipitation unter besonderer Berücksichtigung der Technik, Kolle and Wassermann Handbuch, 1913, 3, 256. Hunt and Mills: Some Experience Bearing on the Medicolegal Value of the Precipitin Test for Human Blood, Boston Med. and Surg. Jour., 1917, 176, 48. Stokes and Stoner: The Use of the Precipitin Test for the Detection of Human Blood in Criminal Trials, Boston Med. and Surg. Jour., 1917, 177, 65.

² Hektoen, Ludvig, The Precipitin Test for Blood, Jour. Amer. Med. Assoc., 1918, 70, 1273.

the foreign protein, will form a precipitate. This reaction is due to the accumulation in the blood of the injected animal of newly produced substances, which are called precipitins. By foreign protein is meant protein from some other source than the species to which the animal injected belongs. Thus serum for the identification of blood is obtained by injecting rabbits (the animal nearly always used for this purpose) with the blood or serum of an animal of a different species, the exact species in each case depending on the kind of blood one intends to test for with the resulting precipitin serum; for the action of precipitin serum is limited to proteins of the same kind as those that were injected; indeed, the precipitin test owes its practical value to this fact.

The Production of Precipitin Serum.—At present we know of only two animals that are good and suitable precipitin producers for practical purposes, the rabbit and the domestic fowl. Hitherto the rabbit has been used almost altogether, Sutherland¹ in India being the only one to use the fowl on a large scale. Of the two the fowl seems to be the more ready and reliable producer, but fowl serum must be handled with special care because of the tendency under certain conditions to give non-specific reactions. So long as rabbits are plentiful, it would seem best, at least in this country, not to change to the fowl except for special purposes, as when it is necessary to test directly for rabbit blood. In any case young, healthy, previously unused animals should be selected; they should be kept under hygienic conditions and given enough of good food. It is always advisable to inject several rabbits at the same time, especially when antihuman precipitin is to be produced, because in some rabbits the response to the injection may be rather insignificant.

Either whole blood, defibrinated or citrated, or serum may be injected; the results appear to be about the same. As we deal with whole blood in the identification of blood spots, there may be advantage in using antiserum produced by whole blood²; this may be counterbalanced, however, by the fact that serum is somewhat richer in proteins. Blood should not be injected intravenously because of the danger of sudden death. To produce antihuman precipitins, albuminous urine and various transudates have been injected also; but the best results are secured from blood or serum, and in these days when patients are bled so frequently from the veins for diagnostic tests, there is no difficulty in obtaining the required human blood or serum, which need not be absolutely fresh provided it is free from bacteria. The injection of rabbits with washed human corpuscles, now so often practised in order to produce hemolytic amboceptor for the Wassermann test, not infre-

¹ Sutherland, W. D., Note on 2643 Medicolegal Cases, in which 6566 Articles, Suspected to be Blood-stained, were Examined, *Indian Jour. Med. Research*, 1915, 3, 205.

² That hemoglobin is antigenic, seems certain. At any rate, strong precipitin serum may be obtained from injecting rabbits with aqueous extracts of carefully washed red corpuscles, this antiserum acting specifically on such extracts and possibly on similar extracts from related species, but not at all or only slightly on the corresponding serums. Hektoen, Ludvig, and Schulhof, Kamil On Specific Erythroprecipitins, *Jour. Infect. Dis.*, 1922, 31, 32.

quently gives as a by-product in sufficient concentration for practical use specific precipitins for the proteins in human blood.

In the immunization of rabbits, good results may be obtained with various methods that differ more or less in minor details. The tendency is to inject smaller quantities of blood or serum than formerly. Several rabbits should be injected at the same time because, as stated, there is great individual variation in the power to produce precipitins, especially antihuman. A good way is to inject from 1 to 2 c.c. of serum intravenously, repeat in six days or so, and then after six or eight days to inject 4 or 5 c.c. intraperitoneally. Or from 5 to 6 c.c. of blood or serum may be injected intraperitoneally four or five times at intervals of six days or so. In either case the serum should be tested about the seventh day or so after the last injection, because about this time the precipitin content reaches its high point; as it remains at this point only a few days the tests must be made promptly so that if the serum is found to be potent, goodly quantities may be collected while the precipitin still runs high. It has been found that the danger of death from anaphylactic reactions when the last injections are given may be avoided by first giving a small so-called desensitizing injection, 1 or 0.5 c.c., intravenously or intraperitoneally.

The intravenous injections of increasing quantities of human serum, say 1, 2, 3, 4, and 5 c.c., at three-day intervals may yield strong precipitin serum also. In this case it is best to begin testing the serum of the injected rabbits as early as the fourth day after the last injection.

A rapid method of immunization consists in giving intraperitoneal injections of increasing quantities—5, 10, 15 c.c.—on three successive days. The same total quantity of antigen injected at one time may also give good results. As a rule, the precipitin in either case reaches its acme about the ninth to the twelfth day or thereabouts. If serum is used, the injections may be made intravenously. This so-called rapid method yields more reliable results with beef, sheep, horse, swine, cat, and chicken blood or serum than with human, and it is probable that in the last case the desired result will be obtained oftener by repeated injections at longer intervals.¹

In the case of the fowl a single intraperitoneal injection of 20 c.c. of blood or serum usually in ten or twelve days yields a precipitating serum of sufficient strength for practical purposes.²

It is not necessary to describe the details of injections, bleeding, and collection of serum. At every step scrupulous effort must be made to prevent contamination; contaminated serum is useless because it may give misleading reactions. Sterile serum may be kept for months in the cold without much loss of potency. It is best to store serum in small bottles or tubes, each of 1 or 2 c.c., so that there need be no

¹ Hektoen, Ludvig, On the Production of Precipitins, *Jour. Infect. Dis.*, 1914, 14, 403.

² Hektoen, Ludvig, The Production of Precipitins by the Fowl, *Jour. Infect. Dis.*, 1918, 22, 561.

danger of contaminating a large quantity each time a little is to be used. A small amount of chloroform may be added as preservative.

Occasionally rabbit serum is opalescent; such serum is useless because when put in test mixtures one cannot tell for sure whether precipitates are formed or not. In order to avoid opalescence of the serum, it is recommended to let the animal fast for eighteen hours or so before it is bled. In the case of the fowl, only roosters should be used, as the serum of hens often cannot be used on account of its fat content.

Tests of Precipitin Serum.—To identify blood or other protein substances it is necessary to use precipitin serum of some degree of potency and of a strictly limited range of action.

Test for Strength.—Various methods have been practised to determine the strength of a precipitin serum, but we shall mention only the



FIG. 84.—Foam test. Persistence of bubbles about ten minutes after blowing through the fluids in Tube 1, which contained a thousandfold dilution of human blood, and in Tube 2, which contained extract of a blood spot of about the same strength. Collapse of all bubbles in Tube 3, which contained pure salt solution.

simple method of finding the highest dilution in salt solution of the antigen—the serum or blood of the species used in the injection—with which the precipitin serum forms a precipitate within a few minutes at ordinary room temperature.

Small, perfectly clean and perfectly clear glass tubes are best, the lumen being about 0.5 cm. in diameter. In each of a series of such tubes in a small rack is placed a small quantity of antigen dilution, the first tube receiving the lowest dilution, the next the next higher, etc. (for example, 1 : 500, 1 : 1,000, 1 : 1,500, 1 : 2,000, etc.); there is now introduced by means of a capillary pipet about 0.1 c.c. of antiserum at the bottom of each tube, special care being taken to get a precise line of contact between the two fluids. The antiserum can be run in slowly at the side of the tube; being heavier than the diluted antigen it will

go to the bottom of the tube, but the line of contact will not be quite so sharp as when it is introduced at the bottom with a pipet. The tubes, which are kept at room temperature, are now watched for the formation of a grayish-white precipitate at the plane of contact between the fluids.

If a precipitate forms almost at once in the antigen dilution of 1 : 1000, the antiserum is strong enough to be used for blood tests for forensic purposes. An antiserum that forms a precipitate almost at once in thousandfold dilution of the antigen usually gives reactions in much higher dilutions—1 : 20,000 or higher after a longer time, say twenty minutes. The strength or titer of antiserum may be designated by the dilution of antigen with which it forms a definite precipitate within a given time, at room temperature. For instance, if an anti-human serum gives a precipitate within twenty minutes in a dilution of human serum or blood of 1 : 20,000, its strength or titer may be said to be 1 : 20,000 at twenty minutes.

The precipitin reaction is observed best by holding the tubes near a black, flat object (book cover, ruler) held directly in the path of the light; the precipitate, at first composed of fine particles, and sharply defined, may become more flocculent and sink to the bottom.

To make tests with dilutions of the whole blood, the corpuscles are laked by means of water; the normal salt content is restored by adding the required amount of 1.8 per cent. salt solution (double the strength of physiologic sodium chlorid solution), and further dilutions are made with salt solution of the usual strength. When fowl antiserum is used, the salt content of all dilutions should be 1.8 per cent., as then there is less danger of non-specific reactions. When fowl antiserum is taken out of the ice box it should be left at the room temperature for an hour or two before it is used.

In place of the contact or ring method, some observers simply mix the antiserum with the antigen; a positive reaction now appears in the form of a diffuse cloudiness of the whole mixture. This method is not as precise and sensitive as the contact method, and is not recommended for practical blood tests.

Tests for Specificity.—On account of the relationships of species, almost every strong precipitin serum may form precipitates with proteins, at least in low dilutions, of species related to that species, the blood proteins of which were used for the production of the serum. Indeed, any strong antimammalian serum may react in low dilutions—1 : 10 or so—of mammalian serums or blood generally. This is the mammalian reaction of Nuttall.¹ In the case of kindred species, the precipitin affinities often are more marked; for instance, an antigoat serum may react in high dilutions of sheep and beef as well as of goat serum or blood. Further examples of closely related groups are the horse, ass, and mule; the dog, wolf, and fox; the domestic fowl, turkey, goose, duck, and pigeon; the hare and the rabbit, each with more or less pronounced common precipitin reactions. Man and

¹ Nuttall, *Blood Immunity and Blood Relationship*, 1904.

monkey, from the highest down, constitute another group with special precipitin interreactions between the members. How it nevertheless may be possible by the precipitin test to identify the blood of the individual species is discussed later. As each antiserum may vary in the number and strength of its group and other precipitins, and as it must be known to be free from non-specific reactions before it is used, it is necessary, besides fixing its potency, to determine the exact range of its action. The test for specificity is carried out in the same manner in general as the test for potency; that is to say, tubes are prepared in the same way with dilutions of as many other serums or bloods beside that used in the production of the serum as seem necessary to afford a thorough test, certainly not less than two, the antiserum added as before, and the results noted. At the same time the antiserum is tested with salt solution only to determine whether any precipitate then forms.

A usable antiserum must be perfectly clear; it must have a certain minimum specific precipitin strength, and it must not give any misleading non-specific reactions. To illustrate: If an antihuman serum is perfectly clear; if it forms a precipitate practically at once in a 1 : 1000 or higher dilution of human blood or serum; and if with that of any other species, then in very low dilutions only, say from 1 : 10 to 1 : 100, and much more slowly, save possibly in the case of the monkey (group reaction); and if it does not form any precipitate with salt solution, then it may be used for tests for human blood for forensic purposes (Table I).

TABLE I

SPECIFICNESS OF PRECIPITIN IN SERUM OF RABBIT INJECTED WITH HUMAN BLOOD

Blood.	Highest dilution giving precipitate with antihuman serum after twenty minutes at room temperature.
Fish.....	1 : 10
Chicken.....	1 : 10
Rabbit.....	0
Guinea-pig.....	1 : 10
Rat.....	1 : 10
Cat.....	1 : 10
Dog.....	1 : 10
Swine.....	1 : 10
Sheep.....	1 : 10
Beef.....	1 : 10
Horse.....	1 : 10
Goat.....	1 : 10
Monkey (<i>Macacus rhesus</i>).....	1 : 100
Human.....	1 : 5000

Preparation of Material for Precipitin Test.—Materials submitted for blood tests usually are stains and spots on any of the great variety of objects on which blood may fall or be smeared (Table II).

TABLE II
PRECIPITIN TESTS FOR BLOOD

Material.	Kind of blood present.	Remarks.
Blood on hat, coat, vest, shirts, and trousers.	Human.	The accused claimed the spots were caused partly by fish, partly by calf blood.
Blood on blade and inside handle of knife.	Human.	
Blood on miner's shirt.	Human.	In this case, efforts had been made to wash away the blood, but deep in the texture of the shirt the threads were still incrustated with blood.
Blood on shoes and shoe-strings.	Human.	
Blood on brick, window shade, coat.	Human.	
Blood on handle of pickax.	Human.	
Blood on hammer and handkerchief.	Human.	
Crust of blood on ax.	Human.	Ax found in ruins of house burned down after triple murder.
Blood on dollar bill.	Human.	
Blood on coat and trousers.	Human.	
Blood on bedclothes.	Human.	
Blood on old newspaper.	Rabbit.	Antirabbit chicken serum used.
Blood on paper money, shirt, trousers, shoes, gun barrel.	Human.	
Smears of blood on the neck of a bottle.	Human.	
Blood on shirt.	Human.	
Blood on shavings.	Human.	
Blood on hair, wall-paper, floor.	Human.	
Blood on shoe-string.	Human.	
Blood on trousers.	Not human.	
Blood on paper.	Human.	
Blood on shoes.	Rabbit.	Antirabbit chicken serum used.
Blood on pocket.	Beef.	Accused worked at beef killing in stockyards.
	Human.	
Blood on wall of barn.	Beef.	The spots were said to have been left by a calf as it ran about after dehorning.
	Human.	

Among the articles submitted by the police to the coroner's office of Cook County, Chicago, for examination of suspected spots and stains, may be mentioned knives, firearms, axes, wrenches, hat-pins, automobile fenders, spades, forks; shoes and gloves; all kinds of wearing apparel, towels, rake, paper, boards, baseball bats, flooring, grass, paper money, stone, mortar, cement, earth, etc. The first question to decide is whether the suspicious spots and stains consist of blood, and for this purpose we have the chemical, microscopic, and spectroscopic methods which have been described. It is necessary to determine whether spots and stains are made by blood, not only because blood may be simulated by paint, fruit juices, and in other ways, but also because spots and stains made by protein materials other than blood may react in the same way as blood to the precipitin test. For instance, antihuman

serum alone will not distinguish spots by human blood from spots by other human protein-containing material such as albuminous urine, purulent sputum, exudates, and transudates. All the antihuman serum can tell us is that the spots are made by human proteins, and whether they are made by blood must be determined by the general tests for blood.

All glassware and other articles used in the precipitin test must be absolutely clean and sterile. It is best in all final tests to use tubes that are practically new, because tubes that have been boiled and sterilized many times may be no longer clear. A good supply of fresh, sterile pipets should be on hand.

Salt solution (0.9 per cent.) is the best general solvent for extracting proteins from material to be tested. If practicable, crusted material may be scraped off, ground up carefully, and mixed with a small quantity of salt solution; or it may be necessary to place small pieces of cloth, paper, or other substances, straw, cork, rubber, wood, leather, lime, mortar, etc., including some or all of a suspected spot, directly into the solution. Whenever possible, extracts should be made also of unspotted parts of the substratum for purposes of control tests. In case of lime-containing material a cloudiness may result that will clear on passing CO_2 into the extract.

How long to continue the extraction depends on the quantity and solubility of the protein in question; if it is to be kept up for more than one or two hours, it is better to put the mixture in the ice box and to add a little chloroform to restrain the growth of bacteria. The passage of protein into solution is indicated if bubbles made by blowing through the fluid with a pipet tend to persist (foam test); also if cloudiness develops on application of the nitric acid heat test. As only a dilute solution—1 : 1000—is wanted for the precipitin test, extracts of blood usually have to be diluted with salt solution. When the nitric acid heat test barely causes a faint opalescence in a blood dilution, its strength is regarded as about 1 : 1000. Comparative foam tests, known blood dilutions being used as the standard, also help to fix the strength of an extract (Fig. 84). A 1 : 1000 dilution of blood is practically colorless by transmitted light. The extracts should be clear as water; turbid extracts must be cleared by filtration or centrifugation. The reaction must be neither strongly acid nor alkaline to litmus; for neutralization, 0.1 per cent. sodium hydroxid or hydrochloric acid solution should be used; dilutions of blood at 1 : 1000 rarely need to have the reaction corrected, but extracts of wood, bark, and leather may contain acids that cause cloudiness in rabbit serum.

Stains that do not extract well with salt solution may give better results if treated with a 1 per cent. solution of potassium cyanid; the alkalinity should be corrected with tartaric acid (Sutherland).

In case of cloth with suspicious stains that yield no information on being scraped or soaked, it is a good plan to cut out small pieces from the stains and tease them apart. The single threads running in the depth of the stained part may be found incrustated with blood, that is,

covered with small crusts which contain red blood-corpuscles or in which the blood is demonstrable in other ways. Even when the cloth has been washed recently, incrustations may be found in the depth, especially, of course, if the cloth is of a heavier sort.

The Actual Test and Controls.—The precipitin test requires a number of careful controls to guard against error; the antiserum must be tested with salt solution, with the blood against which it is known to act, and with other bloods in order to make sure that it gives a specific reaction only. Samples of various kinds of blood should be kept on hand for control tests. For this purpose blood may be dried in drops on filter-paper or linen, each drop being made by a definite quantity (0.1 or 0.05 c.c.); or the blood may be kept in the cold, diluted as described, say 1 : 100 in salt solution. As the reactive power of blood kept in solution is said to weaken gradually, too long intervals must be avoided before new solutions are prepared. To avoid still other chances of error, the extract of the unknown blood must be tested with normal rabbit serum or, if fowl antiserum is used, with normal fowl serum, and extract of blood-free parts of the substratum on which the unknown blood was situated is to be tested with antiserum. These precautions have to be observed in connection with every forensic precipitin test—nothing may be taken for granted. Assuming now that spots on a shirt that have been shown to consist of blood are to be tested for human blood, the precipitin test may be conducted in accord with the scheme presented in Table III, it being understood that the quantity of extract or control solution in each tube is 0.5 c.c. and of antihuman rabbit serum or normal rabbit serum, 0.1 c.c. These quantities may be reduced if desired in order to save material; indeed, the test may be made in capillary tubes if necessary.

TABLE III

SCHEME FOR PRECIPITIN TEST (FIG. 85)

Tubes.	
1	Extract of blood on shirt + antiserum.
2	Extract of blood on shirt + normal serum (estimated dilution of blood in Tubes 1 and 2, 1 : 1000).
3	Extract of bloodless part of shirt + antiserum.
4	Salt solution + antiserum.
5	Human blood or serum 1 : 1000 + antiserum.
6	Blood or serum other than human 1 : 1000 + antiserum.
7, 8, etc.	Same as Tube 6, but with different bloods.

If a typical precipitate (Fig. 85) develops within a minute or two in Tubes 1 and 5 while no precipitate forms in any of the other tubes after standing for twenty minutes, all at the room temperature, then the conclusion is warranted that the blood on the shirt is human blood. Some observers would add, provided monkey blood can be excluded (see final section).

Having obtained a positive reaction with the extract under the aforesaid conditions, it would be well to determine next the highest approximate dilution of the extract that reacts with the antiserum after twenty

minutes at room temperature, thus still further verifying the specificity of the reaction.

Usually the only questions asked are whether certain spots and stains are due to blood, and if so, to human blood; but sometimes it becomes necessary to determine if possible the exact species of blood that is not human. The scheme for human blood is applicable in general with, of course, such changes as to antisera and controls as are indicated in the given case from the facts at hand. If the blood-corpuscles are preserved, it may be possible to determine from the absence or presence of nuclei whether or not one is dealing with mammalian blood. Often tests with various antisera may be made be-

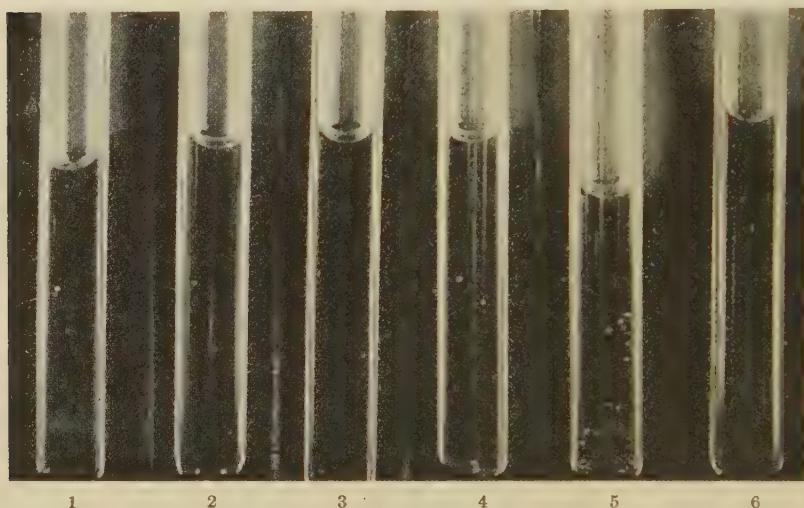


FIG. 85.—Precipitin test for human blood: Tube 1, Extract of blood on shirt of estimated dilution 1:1000 + antihuman rabbit serum; Tube 2, extract of blood on shirt of estimated dilution 1:1000 + normal rabbit serum; Tube 3, extract of bloodless part of shirt + antihuman rabbit serum; Tube 4, salt solution + antihuman rabbit serum; Tube 5, dilution of human blood 1:1000 + antihuman rabbit serum; Tube 6, dilution of sheep blood 1:1000 + antihuman rabbit serum. The precipitates in Tubes 1 and 5 formed almost at once; photograph was taken from five to eight minutes after introduction of the antiserum.

fore a positive reaction occurs, and it must not be forgotten that absence of reaction may be due not only to failure to hit on the right antiserum, but also to changes in the unknown blood whereby it has lost its power to react.

The question whether more than just one kind of blood is present in material to be examined may be raised. It has been found that in mixtures each kind of blood present can be identified by the precipitin test; in such cases, antisera of as high potency as possible should be used, as it may be difficult otherwise to detect proteins present in small amounts.

The claim may be made that a blood-stain which reacts with antihuman serum is not made by human blood, but by the blood of an animal—*e. g.*, dog—falling on clothing or other articles stained before or

afterward with albuminous human urine or some other product containing human protein. In such cases the corpuscles in the stain should be studied with special care to determine, if possible, whether they are consistent in size, shape, and structure with the claims advanced; and then additional precipitin tests should be made as indicated, to wit, with anticanine serum if it is claimed that dog blood is present. In cases such as now assumed erythroprecipitin (antihemoglobin?) serums¹ may prove to be of decisive value if it becomes established that they can act specifically on derivatives from the red corpuscles of different species.

Factors that May Interfere with the Reaction.—The power of blood to react with precipitin may be reduced or completely destroyed by alcohol, by formaldehyd, cresol, corrosive sublimate, and other germicides, by acids and alkalis and other chemicals, by peptic digestion, by decomposition, and by heat. Badly decomposed blood may react, but it is hard to get clear extracts. Fluid blood is said to lose power to react on being heated at from 60° to 90° C. (140° to 194° F.), but dried blood may resist heating at 150° C. (302° F.). Rust also is said to change blood so that it reacts less readily. Blood-stains on shoes blackened over may be detected after neutralization of the solution. In such cases the shoe-strings should be examined carefully; in two instances the accused washed off blood from the shoes but not from the strings. Blood in spots from fifteen to sixty years old has been identified successfully, but certain statements that materials from thousand-year-old mummies may give the precipitin reaction have been contradicted.

Dried blood resists harmful influences much better than fluid, and if blood found in the fluid state is to be kept for tests later on, it is better to dry samples on filter-paper than to keep it in fluid form in which it may decompose. Under no circumstances should blood or bloody material for the precipitin test be put in alcohol, because alcohol causes changes that interfere with the test.

Other Uses of the Precipitin Test.—The precipitin test may be of value also in the identification of bone and other tissue, the origin of which is in doubt, as perhaps only fragments and scraps are at hand. When dissolved, the proteins in and of the tissues give the same general response to the precipitin test as the proteins of the blood of the species concerned. The only exception to this rule is furnished by the crystalline lens, which is unique, as it reacts only to serum produced by injections of lens substance, and that without regard to species. Bone should be reduced to powder, washed thoroughly with ether or benzin to remove the fat, dried, and then extracted with salt solution. Tissue of other nature may be treated according to the same principles. Such extracts are tested in the same general way as blood extracts.

Putting white of egg in urine to simulate albuminuria, and spattering non-human blood on clothing and bedding to feign spitting of blood, have been detected by the precipitin test. The test has been used

¹See footnote 2, p. 928.

extensively in certain European countries to detect adulterations of meat products, particularly sausages, and other foods, as flour and honey; it has been found of value, too, in the administration of game laws.¹

Special Methods for the Differentiation of Blood of Closely Related Animals.—Examples of related animals with more or less common precipitin reactions have been given. In thousandfold dilution a blood may react so much more promptly with its own antiserum than even lower dilutions of related blood that commonly no difficulty arises, provided the limits as to dilution and time are followed exactly as prescribed and the necessary controls included in the test. Nuttall's experiments, to which we have referred, were made according to a totally different plan, the blood dilution being several times lower than 1 : 1000, and the mixtures allowed to stand for several hours. To repeat: A reaction between an antihuman serum and a thousandfold blood dilution is diagnostic of human blood, provided it becomes evident within a few moments and that within twenty minutes at room temperature no reaction occurs between the same antiserum and like dilutions of the bloods selected for the control tests. Sutherland² made a special study of stains by the blood of many varieties of monkeys, his tests being made with the dilutions and time limit just set forth, and in no instance, not even in the case of the orang, did he get a positive result with antihuman serum; consequently, special methods do not seem necessary to distinguish human from monkey blood. These observations should be repeated so that if possible final standards may be fixed. In this country the question whether ape or monkey blood may be present is not likely to arise, because the circumstances, as a rule, preclude that such blood can be present.

That differentiation may be difficult is illustrated by the ruminant group. Antibeeff serum, for instance, may react in high dilution of beef, sheep, goat, and perhaps also other ruminant blood. Indeed, any antiruminant serum may react with any ruminant blood in considerable dilution, although not with equal promptness in all cases. Several expedients have been recommended in this and similar cases:

1. **Specific Absorption** (Weichardt).—This is based on the principle that by mixing, let us say, antibeeff serum with goat serum and then removing the resulting precipitate, the special antig goat precipitin will be removed.

2. **Cross Immunization** (Uhlenhuth).—This consists in obtaining precipitin serum from one animal for the proteins of a related animal. Injecting certain Old World monkeys with human serum, Uhlenhuth

¹ Gay, A Contribution to the Forensic Value of the Musculoprecipitin Test, Jour. Med. Research, 1908, 19, 219. Clarke, Forensic Value of the Precipitin Test in the Enforcement of Game Laws in California, Univ. of California Publications in Pathology, 1914, 2, 131.

² Sutherland, The Applicability to Medicolegal Practice in India of the Biochemical Tests for the Origin of Blood-stains, Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India, 1910, 39.

obtained antihuman precipitins, but this result seems to be quite exceptional, as neither Sutherland¹ nor Berkeley² were able to confirm it. Uhlenhuth was able to demonstrate hare blood on a cane by means of antihare precipitins developed in the rabbit, antihare fowl serum reacting equally well with hare and rabbit blood; he also found that the fowl produces antipigeon precipitin and the pigeon antifowl, but cross immunization failed in the case of the horse-ass, and goat-sheep.

3. Dilution of the Antiserum and of the Suspected Blood.—Dilution of an antiserum may so weaken certain confusing group precipitins as to cause their practical elimination and still leave the main precipitins strong enough to give a specifically diagnostic reaction under the conditions prescribed for forensic practice. For diluent, Sutherland and Mitra³ recommend normal serum of the same kind as the antiserum.

It is, of course, in the low blood dilutions that antisera of high potency give the most marked group reactions. As the dilutions of the bloods of a group are increased, the reaction narrows down more and more, and in high dilutions there may be no question as to its specificity. Hence, determination of the highest dilution in which a suspected blood reacts with a given antiserum, if properly controlled, may solve the problem.

4. Special Study of Rapidity and Measure of Reaction.—Hamburger⁴ recommends that in the case of a stain that reacts with antiruminant serum, for instance, separate parts of the extract be tested with antigoat, antisheep, and antibovine serum in the usual way, and the results carefully noted. The antiserum that gives the most rapid and profuse precipitate supplies the clue.

Systematic detailed studies should be made on the blood of closely related animals in order to determine more fully to what extent differentiation can be made by these and possibly other methods.

Suggestions to the contrary⁵ notwithstanding, it is not possible to distinguish between different human races, and far less between individuals, by means of the precipitin test.

¹ Loc. cit.

² Berkeley, The Impossibility of Differentiation Between Monkey Blood and Human Blood by Means of Antisera Derived from Monkeys, Univ. of California Publications in Pathology, 1913, 2, 105.

³ Sutherland and Mitra, Misleading Reactions Obtained with Precipitating Antisera, and How to Avoid Them, Indian Med. Jour., 1914, 1, 707.

⁴ Hamburger, *Gerechtig onderzoek van bloed en anders lichaamsvochten*, Tijdschr. v. strafrecht, 1904, 17, 82. Zur Differenzierung des Blutes (Eiweiss) biologische verwandter Tierspecies: eine Erweiterung der üblichen serodiagnostischen Methode, Deutsch. med. Wchnschr., 1905, 31, 212. Here it may be noted that Welsh and Chapman have pointed out that the weight of the precipitate under certain conditions serves to distinguish between related proteins. Welsh and Chapman, On the Differentiation of Proteins of Closely Related Species by Precipitin Reaction, Jour. of Hyg., 1910, 10, 177.

⁵ Mallet, The Serum Precipitation Test for the Identification of Blood-stains, Virginia Med. Semimonthl., 1903-1904, 285; Tr. Med. Soc. Virginia, 1903, 1904, 49. Bruck, Die biologische Differenzierung von Affenarten und der menschlichen Rassen durch spezifische Blutreaktion, Berl. Klin. Wchnschr., 1907, 44, 798.

MEDICOLEGAL APPLICATION OF HUMAN BLOOD ISO-AGGLUTINATION

The inheritance of the iso-agglutinative group-specific substances in human blood appears to follow mendelian laws and blood grouping may prove of value in questions of parentage.¹ If the child's blood belongs to the correct group for the alleged parents, it may be their offspring, but if the child's group is wrong as concerns the alleged parents, it must have a parent other than one of those claimed. Buchanan² regards these criteria as unsafe because of the possibility that the heterozygous status of a parent might result in the appearance of the child of an unexpected but wholly legitimate group.

The possible value of iso-agglutination tests in efforts to trace blood spots back to the person from whom they came, should not be overlooked. If the blood can be shown to belong to the same group as that of the person in question, it may be his or her blood, but if it belongs to a different group it must be the blood of a different person.

¹ Ottenberg, Medical Application of Human Blood Grouping, Jour. Amer. Med. Assoc., 1921, 77, 682; 1922, 78, 873. Hereditary Blood Qualities, J. Immunol., 1921, 6, 363.

² Medicolegal Application of The Blood Group, Jour. Amer. Med. Assoc., 1922, 78, 89; 79, 180.

MEDICOLEGAL EXAMINATION OF SEMINAL STAINS¹

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THE recognition of a seminal stain on clothing or other substance naturally may be of great medicolegal importance in cases of alleged rape or sodomy. The variety of substances liable to be submitted for examination for seminal stains is not so great as for blood-stains. The articles usually brought are pieces of bedclothing or underclothing, and sometimes other apparel; in some cases scrapings from the skin or mucous membrane of the alleged victim, such as dried masses from the neighborhood of the genitals or adherent to the hair, or scrapings of mucus from the vagina. Rarely extraneous substances, such as pieces of wood, metallic instruments, or bits of leaves or earth are submitted for examinations of this kind. Seminal stains, like blood-stains, may be either simple or complex—that is, they may consist of pure dried seminal fluid or of seminal fluid mixed with other fluids or secretions, such as blood, discharges from vagina or intestines.

Seminal fluid varies somewhat in its consistence according to circumstances, and in the same individual at different times. Its density may vary from 1027 to 1037; it is more or less viscid and feebly alkaline; usually it has a grayish, more or less opalescent appearance, and in rare instances it may have a reddish tint, even when not mixed with blood, and more particularly is this the case in old age. When fresh, it has a peculiar odor that is entirely lost on drying. Formerly considerable importance was attached to the odor as a medicolegal test, but at the present time this test is never employed in dried stains, as many other substances have been found that, particularly when heated, yield an odor closely resembling that of heated seminal fluid.

The appearance of a dried seminal stain varies according to circumstances, and particularly according to the nature of the surface on which the stain is made. If on a non-absorbent surface, such as a piece of wood or iron, or on heavy woolen cloth or velvet, it dries, forming a grayish scale on the surface, from which a portion can be removed easily with the point of a knife-blade or a needle for microscopic examination. If cotton or linen cloth has been starched, so as to render it comparatively non-absorbent, a seminal stain will have the same scaly appearance. The color of the stain may be simply grayish or have a faint yellowish tint, and in old men the stain may have a reddish tint. On unstarched cotton, linen, or any absorbent fabric a seminal stain

¹ This article, in its present form, is a revision and expansion of that appearing in the first edition and written by the late Dr. Edward S. Wood.

is difficult to see, especially if the stain be a small one. When a drop of the fluid falls on such a fabric, it is immediately absorbed, and the fluid portion extends for quite a long distance, forming, when dry, a nearly colorless stain having an irregular outline. In some instances scarcely any change in color is produced on the surface of the cloth, but if the cloth be viewed by transmitted light, the stained portion will be somewhat translucent, the meshes of the cloth being more or less filled with the dried material. The stained portion will also be found to have a stiffer feel than the unstained portion of the cloth, as is the case when such a fabric is stained with blood or an albuminous fluid. If the seminal fluid forming a stain is mixed with other secretions, the appearance of the dried stain would, of course, be modified accordingly.

The location of seminal stains may vary greatly with different circumstances. In cases of alleged rape they are found most frequently on the underclothing of the victim or on the clothing of the accused. In cases of rape of young girls the stains are almost invariably found on the posterior flap of the undergarment or on the drawers or shirt. On the undergarments of men the stains are almost invariably on the anterior portion.

The Florence Test.—Seminal stains are detected with absolute certainty only by the recognition of the characteristic morphologic elements, the spermatozoa, by microscopic examination. The seminal fluid consists of an admixture of the secretion of several glands, being a solution of various organic and inorganic substances, especially rich in phosphates, and the characteristic spermatozoa and numerous cells coming from the mucous membranes lining the different portions of the seminal tract. The seminal fluid contains nucleoproteins, albumin, and a proteose-like substance. A crystalline substance called spermin was first isolated from seminal fluid by Schreiner in 1878. It is said to have the formula C_2H_5N , and gives all the general reactions of an alkaloid. It is soluble in water and absolute alcohol, but very slightly soluble in ether; its solutions have an alkaline reaction. Spermin is not peculiar to the seminal fluid of man, but has been found in that of some animals, also in sputum, blood, and some of the animal tissues. The views as to the nature of this base are not unanimous. Florence¹ claims to have discovered an alkaloidal body that he finds only in the seminal fluid of man, and that gives a characteristic crystalline precipitate with a concentrated solution of iodine in potassium iodide. Florence has not been able to obtain these crystals with the seminal fluid of any other animal, nor from any other fluid or tissue. This substance Florence calls *virispermin*. This test is one of extreme delicacy, a single fibril of cloth upon which is a dried seminal stain sufficing to yield numerous crystals when the test is properly made.

The reagent consists of:

Potassium iodide.....	1.65 gm.
Iodine.....	2.54 "
Distilled water.....	30.00 "

¹ Du Sperme et des Taches de Sperme en Médecine Légale, 1897.

These proportions correspond to the formula KI_3 . The iodine dissolves quickly in the solution of potassium iodide, and it is only necessary to mix the materials together in a glass-stoppered bottle and allow it to stand for a short time, when the reagent will be ready to use.

The test is made in the following manner: A minute fragment of the stained fabric is carefully removed by fine-pointed forceps and sharp-pointed scissors, transferred to a glass slide, treated with a small drop of distilled water, allowed to soak for a minute or two, a minute drop of the iodine reagent added to it in such a way that the two drops of fluid come in contact by their edge, and immediately covered with a cover-glass. If the suspected stain contained any dried seminal fluid, the examination with the microscope will show a very large number

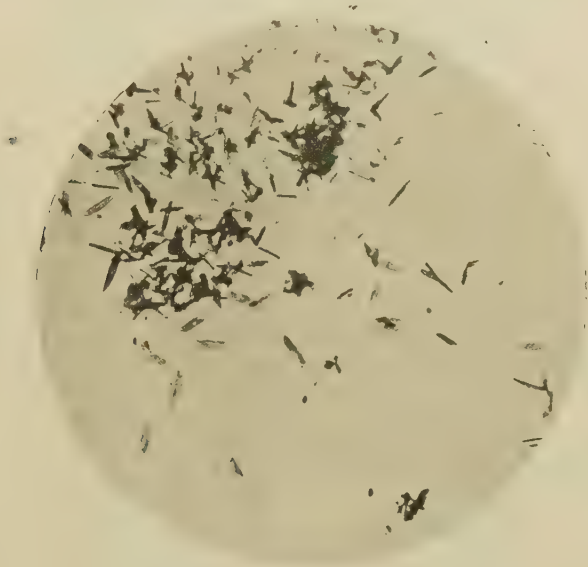


FIG. 86.—Seminal crystals (small) ($\times 750$).

of brown crystals that resemble in appearance the hemin crystals obtained with Teichmann's test with blood. Figures 86, 87, and 88 show these crystals, obtained from a single thread $\frac{1}{8}$ inch long cut from the stained portion of a pair of child's drawers in a case of attempted rape, the stain being three years and four months old at the time the test was made.

If the stain be on a non-absorbent surface, like a piece of wood, it is sufficient to remove a minute fragment of the scale with the point of a knife, transfer to a glass slide, and treat in the same manner.

This test, while it is not all that Florence claimed for it, is extremely valuable as a preliminary test. It has the same value as a preliminary test for seminal stains that the guaiacum test has as a preliminary test for blood-stains. If the characteristic crystals are obtained in any

given stain, it shows that the stain may be a seminal stain, and an examination must be made for the detection of the spermatozoa, which



FIG. 87.—Seminal crystals (medium size) ($\times 750$).

must be found also in order to be able to state with certainty that the stain in question is a seminal stain. If, however, no crystals are obtained with this test with any given stain, it shows with certainty that



FIG. 88.—Seminal crystals (large) ($\times 750$).

the stain does not contain any dried seminal fluid. In treating an ordinary seminal stain in this way, as a general rule, a brown precipitate can be seen to form at the instant that the two drops come in contact

upon the glass slide, and this brown precipitate, on microscopic examination, is seen to consist of the characteristic crystals.

The Barberio Test.—With an aqueous solution of picric acid added to newly voided, putrefied or macerated semen, Barberio obtained yellow microcrystals like needles, of rhomboidal shape, three or four times as long as wide. Occasionally forms like two cones with bases together appeared. The crystals can be preserved on the slide after removing the excess of picric acid with distilled water, absorbing the water with filter-paper, and mounting in balsam. The reaction may be obtained with stains as old as six years, and probably after a longer time. If the stain has been submitted to a temperature higher than 150° C. (302° F.), a poor reaction is obtained; at 200° C. (392° F.) crystals cannot be obtained.

Lecha-Marzo,¹ who gives an extended review of the whole subject, tested fresh and putrefied brain, liver, kidneys, lungs, spleen, nasal, and vaginal discharges, blood, pus, perspiration, white and yolk of eggs, and some vegetable juices with Barberio's method and obtained negative results. With saliva rounded crystals were obtained but they were easily distinguished from those of semen.

While many methods have been proposed for obtaining crystalline precipitates, none seem to be absolutely specific for semen. Thus crystals are produced on the addition of the Florence reagent to solutions of the decomposition products of lecithin, which is one of the constituents of many animal tissues. Lecithin decomposes during putrefaction or drying, so that the Florence reaction may be obtained with extracts of tissues that contain lecithin if they have decomposed and are old. This does not, however, detract from the value of the test as preliminary test, and it remains the most valuable of any chemical test recommended so far for seminal stains. For the positive recognition, however, of a seminal stain it is necessary to obtain perfect spermatozoa.

Detection of Spermatozoa.—The spermatozoa, as is well known, are tadpole-shaped bodies having an ovoid head and a tail nine or ten times longer than the head. The length of the head of human spermatozoa is very constant and about $\frac{1}{3000}$ inch, being, therefore, as long as the diameter of the human red blood-cell. If seen on its side, the head of a spermatozoön appears more or less pear shaped. In the examination of stained spermatozoa it will be seen that the anterior third of the head is less dense than the posterior two-thirds, and is stained less deeply. This is well shown by Fig. 89.

The spermatozoa are stable and not readily destroyed, so that they may be detected in stains many years old if the stain has not been subjected to too much washing or exposure, as shown by Fig. 90 of a spermatozoön isolated from the seminal stain three years and four months old on a child's drawers. These bodies are, however, after they become dry, very brittle, so that the tail is easily separated from the head, and it is for this reason that it is so difficult to

¹ *Progresos de la Clinica*, 1918, 6, 267.

obtain many perfect spermatozoa in the examination of old dried seminal stains.

For the positive recognition of spermatozoa it is necessary to find the perfect bodies with head and tail complete, since there are other bodies, such as certain spores, sometimes found in old stains, which much resemble the heads alone, and there are numerous substances, such as bacteria or bits of the fibrils of cloth, which frequently resemble the tails alone. Therefore great care should be exercised in the handling of any substance suspected to contain seminal stains which are to be submitted for medicolegal examination. They should not be subjected to unnecessary handling or rubbing, and should be submitted in as fresh a condition as possible.

If the stain is a scaly one, as by the drying of the fluid on a non-absorbent surface, the detection of the spermatozoa is comparatively

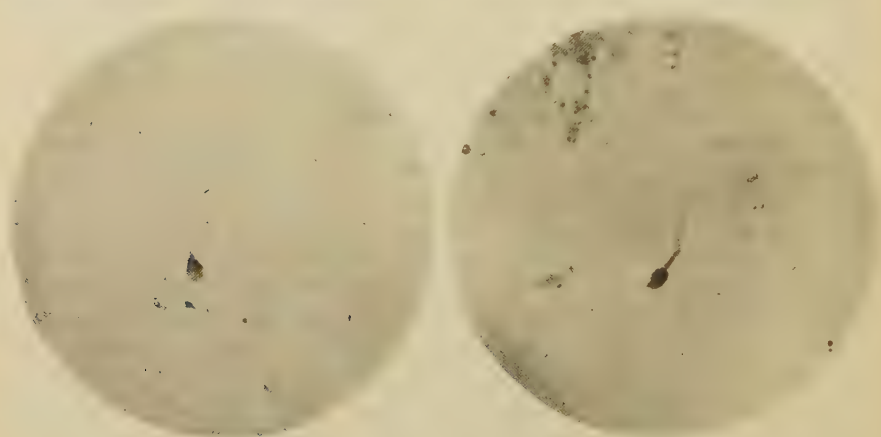


FIG. 89.—Human spermatozoön: fresh specimen dried on glass.

FIG. 90.—Human spermatozoön: from old stain on cloth.

easy. A fragment of the stain, removed with the point of a knife, should be transferred to a glass slide, treated with a drop of distilled water, and allowed to soak for several hours under conditions that will prevent the rapid evaporation of the water. The scales should then be gently separated with fine needles, treated with a drop of the staining solution, covered with a cover-glass, and examined directly with the microscope. Sometimes a better preparation can be made by first soaking the particles of stain with water on a cover-glass for several hours, then pick to pieces, and allow to dry. When dry, pass the cover-glass three or four times through a flame, or heat it in an air-bath to 115° C. (239° F.) for fifteen or twenty minutes, so as to fix the spermatozoa on the glass, in the same way that blood-cells are fixed previous to being stained. Then treat the dry residue on the cover-glass with staining solution, wash off the superfluous stain, and dry. This preparation can be mounted dry, sealing the cover-glass with paraffin, or it can be mounted in Canada balsam, or in any desirable menstruum.

If the stain is on unstarched cotton or linen cloth, the detection of the spermatozoa is much more difficult. The spermatozoa are apt to cling to the fibrils so tenaciously that it is difficult to separate them without breaking the head from the tail. Care should be taken to select for the examination a thread of the cloth near the center of the stain, and the cloth should first be examined with the lens in order to see, if possible, if one side contains more dried stain than the other. For instance, stains have been found that yielded an abundance of spermatozoa on one side of the cloth, while none could be found on the other, although the Florence reaction could be obtained on both sides. Also the fluid portion of the seminal fluid may be sucked along for quite a distance on a piece of linen or cotton cloth, while the solid bodies, the spermatozoa and cells, may be limited to near the center of the stain; in this case the Florence reaction will be obtained from the edge of the stain as well as from the center, but the spermatozoa can be isolated only from the central portion of the stain.

The best method to prepare such a stain for microscopic examination is carefully to cut from near the center of the stain, with a pair of fine-pointed scissors, a few individual threads of cloth from $\frac{1}{16}$ to $\frac{1}{8}$ inch long, and treat each piece of thread on a glass slide or cover-glass with a small drop of water, allowing it to soak at least two hours, the evaporation of the water being prevented. Some think that the soaking should continue from twelve to twenty-four hours. Numerous preparations should be made, since it frequently happens, even in well-marked seminal stains, that careful search will fail to detect unbroken spermatozoa in one or more of the preparations. After sufficiently prolonged digestion the small fragment of thread should be very carefully separated into its individual fibrils by manipulating with sharp-pointed needles. It can then be stained and examined.

To prevent the breaking of spermatozoa on cloth Wondson¹ recommends that the cloth be fixed in Müller's fluid for twenty-four hours at 37° C. (98.6° F.), washed in several changes of water, blotted, and laid flat on a slide, drying the slide slowly and staining with 1 per cent. watery solution of eosin, washing, and drying. Hankin² suspends the stained cloth for a moment in boiling water, cools, places it in a 2 per cent. potassium cyanid solution for two minutes, washes in distilled water, and teases out the threads on a slide before mixing and staining.

Bacchi³ proposed a staining method for cloth as follows: Place the piece of cloth, say 1 cm. square, in 1 per cent. acid fuchsin or methylene-blue; wash in 1 per cent. hydrochloric acid; dry in air or dehydrate in absolute alcohol; clear in xylol, mount in Canada balsam. If the spots are not fresh put for one-half hour to twenty-four hours in 20 to 30 per cent. ammonium hydroxid solution and then in distilled water.

Ellerman⁴ stains an isolated thread with erythrosin, places it in

¹ Brit. Med. Jour., 1908, 2, 501.

² Ibid., 1906, 2, 126.

³ Vrtljschr. f. gerichtl. Med., 1912, 43, 1.

⁴ Ibid., 1911, 42, 116.

ammonia water for one minute, washes in water, then stains in iron hematoxylin for two minutes, dries and mounts in balsam. The spermatozoa are black; the fibers not stained.

Moist material, such as mucus obtained from the uterus or vagina, may be placed upon a glass slide, stained, and examined at once for the detection of spermatozoa.

According to Florence, the spermatozoa of none of the domestic animals have the pear-shaped profile that human spermatozoa have.

The following table by Boston¹ gives the measurements of various spermatozoa in microns:

	Total length.	Heads.		Tail length.
		Length.	Width.	
Man.....	51-58	4-6	3-4	41-53
Dog.....	67-74	4-8	3-4	59-67
Rabbit.....	51-66	6-9	3-4	45-60
Horse.....	64-67	6-8	6	54-60
Bull.....	87-93	9	6	77-83
Sheep.....	83	9	3	74
Cat.....	58-74	7	3-4	53-66

The Biologic Test.—Farnum² has proposed a biologic test for human semen that is based on the same principles as the serum test for blood. He prepared rabbits by injecting into the peritoneal cavity from 5 to 10 c.c. of either semen or testicular emulsion at intervals of from two to six days, the rabbit receiving from 5 to 8 injections. The test was made in a similar manner to the serum test for blood. He found that the serum obtained from the blood of rabbits prepared with human semen gave a distinct reaction with both recent and old emulsions of human semen in salt solution, and also with human seminal stains which have been dried and kept for thirty-four days, these stains being extracted with salt solution and filtered. More recent observations by one of us³ tend to confirm Farnum's results, as they indicate that there is a specific antigenic substance peculiar to human semen. Whether this precipitin reaction or other immune reactions, such as the anaphylactic test suggested by Lecha-Marzo, are practicable for the detection of semen in medicolegal work, remains to be demonstrated. At present the precipitin test holds out promise enough to merit thorough trial.

¹ Jour. Applied Microscopy, 1901, 4, 1360.

² C. G. Farnum, Biologic Test for Semen, Jour. Amer. Med. Assoc., 1901, 37, 1721.

³ Ludvig Hektoen, Specific Precipitin Test for Human Semen, Jour. Amer. Med. Assoc., 1922, 78, 704.

MEDICOLEGAL EXAMINATION OF HAIRS

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A NUMBER of questions present themselves in connection with the medicolegal examinations of hairs, among the most important of which are the following:

1. Is the material examined hair or some other fiber?
2. If hair, from what animal did it come?
3. If the hair is human, can it be identified as the product of a given individual?
4. If of human origin, from what part of the body did the hair come?
5. What was the age of the person from whom the hairs were derived?
6. How were the hairs removed from the body?

The first question is usually easily answered. It is true that to the naked eye various articles, chiefly vegetable fibers, may simulate hairs; but by the aid of the microscope all other bodies may be distinguished from them.

The distinctive features of hairs that are recognized by even low powers—200 to 300 diameters—are: 1. The shingled or terraced ("imbricated") surface. 2. The distinction between cortex and medulla. 3. The pigment granules in the cortex. 4. The cells composing the medulla. 5. The transition in structure from shaft to root, and the peculiar sheath of the latter.

It is seldom that all these features are found in a single specimen submitted in a judicial inquiry; but, fortunately, positive identification can be made through the detection of several of them.

If needed, confirmation of the identity can be secured by submitting the supposed hair to certain chemical reagents; a strong mineral acid, heated, causes the disintegration of a hair into the component cells.

The bodies from which hairs must, by these features, be distinguished are cotton, linen, silk, wool, and vegetable fibers (Fig. 91). Cotton is a flat, tape-like fiber with a tendency toward a spiral twist; linen is a jointed, bamboo-like fiber with transverse markings at irregular distances; silk is a cylindric fiber without markings, but strongly refractive. Wool, as a variety of hair, presents the imbricated surface characteristic of hairs, while in general cylindric, its diameter varies in different parts. Any of these fibers may, of course, present the colors imparted by the dyes used in the cloth.

The second question is from what animal the hairs have been separated. Fortunately, the query does not usually include the whole catalog of hairy animals; else the solution of the problem might become

practically impossible, because of the great similarity between individual hairs of different species. Practically the only animals requiring consideration are those which, living or dead, enter into human environ-

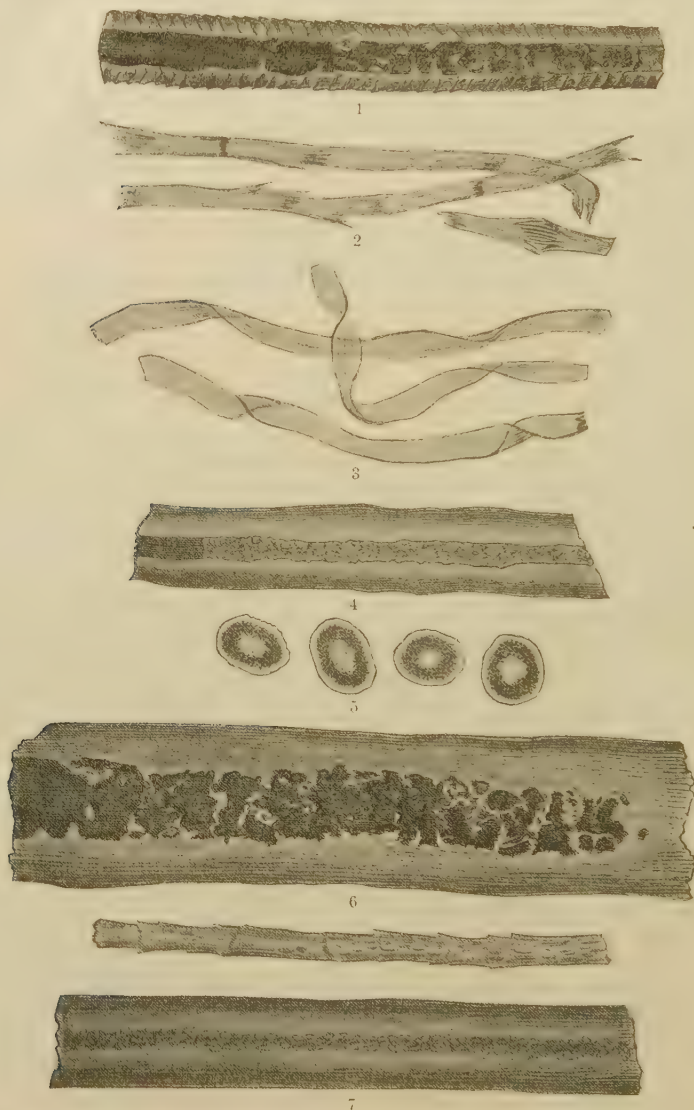


FIG. 91.—1. Sheep's wool ($\times 200$). 2. Linen fibers ($\times 200$). 3. Cotton fibers ($\times 200$). 4. Hair from human head ($\times 200$). 5. Transverse sections of hairs from human head ($\times 200$). 6. Hair from human beard ($\times 200$). 7. Hairs from back of hand ($\times 200$).

ment—the domesticated quadrupeds, the parasitic rodents, the animals whose skins are converted into clothing. The hairs of these represent different types, and can all be distinguished positively from human hair (Figs. 91, 92).

The third question often presented to the microscopist in a legal inquiry is whether hairs admittedly human can be identified as the product of a given individual; whether they must have grown on the body of a certain person, and could not have been furnished by any other.

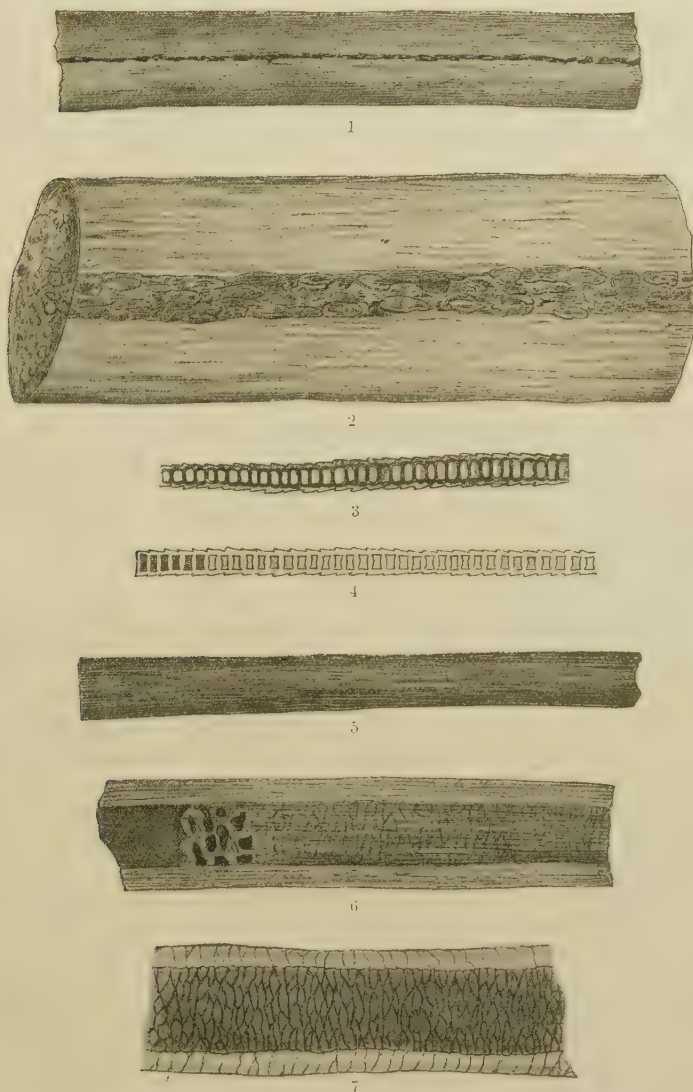


FIG. 92.—1, Hair of ox ($\times 200$). 2, Pig's bristle ($\times 200$). 3, Cat's hair ($\times 200$). 4, Mouse's hair ($\times 200$). 5, Horse's hair ($\times 200$). 6, Donkey's hair ($\times 200$). 7, Goat's hair ($\times 200$).

This question must be answered always and distinctly in the negative. While similarity in color and size with that of a given individual may be marked, there is nothing peculiarly characteristic in the hairs of

one person to distinguish them from the hairs of many others of similar complexion. It may occasionally happen—as in one case examined by the writer—that the hairs in question present certain peculiarities of structure due to disease; the detection of similar abnormalities in hairs from the suspected source would naturally furnish a probability, but not a certainty, of a common origin. Aside from these necessarily rare cases, identification of the individual from whom given hairs are derived is dependent upon community of size, length, and color; and these are insufficient to warrant more than a probable conclusion.

A fourth question is, From what part of the human body are the hairs under examination derived? This question may often be answered definitely because of the following facts:

1. The long, soft hairs from the scalp and beard are distinguished both by their length and by their gradual tapering from root to point.

2. The short, thick, stiff hairs from the eyelashes and the eyebrows, while averaging almost the same thickness as scalp hairs at the root, taper rapidly toward the point.

3. The short, slender, flexible hairs from the general surface of the body—the so-called lanugo or down—have, on the average, a much smaller diameter than other hairs, even than the equally short but thick hairs from the eyelashes. These downy hairs, moreover, frequently exhibit no pigment granules in the cortex; and the medullary canal is apt to be relatively small and is frequently absent.

The average diameters of hairs from different parts of the body may be approximately stated as follows:

Scalp hairs, $\frac{1}{350}$ inch in the male, $\frac{1}{450}$ inch in the female; the variations in different persons may, however, be extreme—from $\frac{1}{1000}$ to $\frac{1}{200}$ inch, for example.

Hairs from the beard and mustache are usually the thickest of the body, ranging from $\frac{1}{250}$ to $\frac{1}{150}$ inch; they usually exhibit the greatest diameter on the chin and upper lip, shading off in diameter as they approach the scalp above and the neck below.

Hairs from the eyebrows, lids, axillæ, and pubic region present about the same diameter at their roots as do those of the scalp; though here again great variations are found in different individuals.

The downy hairs from the general body surface are notably less in diameter than those in the so-called hairy parts of the body; they average from $\frac{1}{2000}$ to $\frac{1}{1000}$ inch in diameter near the root.

A fifth question sometimes propounded to the expert microscopist is, What was the age of the person from whom the hairs were derived? Here again his answer is restricted by serious limitations, and must be based upon the application, to the question at issue, of the following facts:

The downy hairs of the fetus and of the newborn infant contain no pigment and no medullary canal.

The hairs of children before puberty frequently have no medullary canal; they are relatively slender when compared with hairs of the same length and locality from adults.

A sixth query to which an answer may be sought through the microscope is, Were the hairs forcibly pulled out, shed from natural causes, or cut off?

This question can be answered, as a rule, decisively on the following facts: The root of a growing hair is concave, fitting over the convex papilla from which it grows. When forcibly separated from the head, the root end shows this concavity, as a rule; a bunch of hairs, most of which exhibit this feature, may with certainty be affirmed to have been forcibly pulled from the body. On the other hand, hairs which have fallen from natural causes exhibit little or no concavity at the root end.

A hair which has been cut from the head or other part naturally shows a plane surface, or something approximating this, where the cutting instrument severed the hair. The cut surface is sometimes uneven, because the different fibers composing the shaft have been severed at various levels.

The hairs growing upon the human body may be considered in three categories:

1. The long, soft hairs from the head.
2. The short, stiff, thick hairs from the eyelashes.
3. The short, slender, flexible hairs from the general surface of body and face—the so-called lanugo or down.

The long hairs from scalp and beard are naturally the most frequent subjects of microscopic examination for judicial purposes; in rarer cases the downy hairs, overlooked perhaps by naked-eye examination, have been magnified by the microscope into formidable witnesses of guilt. In one case in which the writer was engaged the presence of these diminutive hairs in blood-stains on a knife strongly confirmed the inference, from measurements of the blood-corpuscles, that the blood was of human origin.

In all cases where the identity of hairs is to be determined it is extremely desirable that several hairs be obtained for examination; because some of the structural peculiarities upon which the recognition of the animal source depends may be absent in any single hair. Thus the medulla of human hairs—whose appearance and relative diameter to that of the entire shaft are important features—disappears in some sections of the hair, especially near the point; the pigment-granules also, whose size and distribution are characteristic of human hairs, may be nearly or quite lacking in individual specimens.

The domestic animals whose hairs approach most nearly in structure those from man are the dog and cow; yet the distinction is rarely difficult to one familiar with them all.

Thorough study of the structural peculiarities of hairs from all available sources must precede the attempt to identify given hairs in a judicial inquiry.

The usual method of preparing hairs for microscopic examination is to wash thoroughly with water, dry carefully, immerse in turpentine oil, and mount in Canada balsam.

MEDICOLEGAL RELATIONS OF THE *x*-RAYS, RADIUM, AND ULTRAVIOLET RAYS

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RADIANT energy is of forensic importance because of the use which is made of it in medicine, both in the diagnosis and treatment of disease and the liability of certain untoward results from its application. It had long been known that there were invisible rays at both ends of the spectrum. It was not, however, until 1895 that Roentgen demonstrated that certain rays had the power of penetrating opaque substances. From that period there has been an increasing knowledge of radiant energy. It is now believed that such radiations are electromagnetic phenomena, but as to the exact character of the rays nothing more definite is known. The rays of the visible spectrum are comparatively short, having a length of $\frac{1}{4}$ to $\frac{1}{2}$ inch. The invisible spectrum contains rays of inconceivable shortness and some of great length, up to or beyond a thousand feet. The best known of these effects of the invisible rays are the ordinary phenomena of sunburn. Of course it is not a burn at all in the sense that it is produced by heat. It is caused by ultraviolet rays from what is known as the "cold" part of the spectrum. It is well known that there is a markedly varying susceptibility. Individuals under like circumstances of exposure to the sun are variously affected; some being unaffected, others suffering from severe burns with vesication even of a comparatively brief exposure.

x-RAYS

The *x*-rays travel in straight lines with the velocity of light. They produce a marked reaction on a photographic plate, but like the rays of visible light they are not homogeneous, but are composed of waves of different lengths. One of their most remarkable characteristics is the ability to penetrate substances inversely as their atomic weights, the shorter waves penetrating most deeply.

Two principal types of tubes are used for the production of these rays: the gas and the Coolidge tubes. The latter is exhausted of air so far as possible, while a small amount of air or other gas is necessary for the successful operation of the gas tube. A suitable current applied to a gas tube causes the ionized gas to leave the cathode and travel to the anode at a high rate of velocity. This stream is known as the cathode ray. At the target upon which the stream is focused the electrons are suddenly arrested, giving rise to electromagnetic waves

which travel in all directions from the target; these are known as x -rays. The Coolidge tube exhausted to as low a pressure as possible supplies the electrons from the hot cathode. The physical effects regardless of the character of the tube are the same, though for certain purposes tubes of different construction will give better results. The radiodental type of Coolidge tube is designed for dental work in making radiographs of teeth and jaws and is not suitable for general work.

In practice roentgenology is divided into three branches: Radiography, fluoroscopy, and roentgenotherapy.

Roentgenography is a method of physical diagnosis by means of Roentgen rays and a photographic plate or film. A roentgenogram is a photographic negative produced by these rays which is extensively used in the diagnosis of disease.

Fluoroscopy is a process of inspection by means of a fluorescent screen which is commonly mounted in an instrument called a fluoroscope.

Roentgenotherapy is now firmly established as a method of treatment. It has been shown that the x -rays have a destructive action upon tissues of low vitality, and that they also have a property of stimulating normal cells to greater activity. It is upon this property that the principal therapeutic action is based. The use of the Roentgen rays for treatment requires careful study and experience. If the time of the application be too short the diseased cells may be stimulated to greater activity, or if, on the contrary, the application be too long, the normal cells may be injured, or what is commonly called an x -ray burn be produced. Certain terms have been employed in reference to radiographs which are erroneous. For instance, it is improper to speak of the destructive action of the x -rays as a burn in the sense that the term is used to describe the effect of heat. The courts frequently speak of x -ray photographs, a term that is equally faulty, as they are not produced by the action of light. This erroneous term leads jurors and others to regard the appearances on an x -ray film as comparable in many respects to a photograph. They are not in any sense photographs, but are pictures of shadows, and if the term shadowgraph or skiagraph were used, it would give a much clearer idea of the manner in which these pictures are produced, and would perhaps afford the public a better idea of their value. There is little doubt but what this failure to understand just how these pictures are produced leads to many misconceptions of their value as evidence.

The probability of distortion in taking these pictures is recalled by the parlor plays in which shadows are thrown upon a screen, the sole source of light being behind the object causing the shadow. The familiar and grotesque effects produced in these shadows by a slight change in the position of the object or in the source of the light is well understood. The same mechanism is called into play when a radiograph is taken. If the plate is moved a slight distance from the object there is immediate alteration of the shadows and their relations. The same is true if the tube is moved. Radiographs have shown what

appeared to be fractures where none existed. In other cases a demonstrable fracture showed no signs of a break on radiographing. The callus which is thrown out about a fractured bone is very translucent and may show a space which resembles a fracture; at the same time the bone may have sufficient strength to bear the weight of the body.

A skiagraph needs to be interpreted properly with due regard to limitations; hence, allowing it to go to a jury without explanation may lead to an erroneous interpretation. Even surgeons who are familiar with the normal relations of joints may fail in interpreting a radiograph. Those who are best skilled in estimating the value of radiographs are a unit in the opinion that they should be taken only by skilled operators and their interpretation should be in the hands of someone who has had practical experience in radiographic work. This is no argument against their admissibility in evidence, but simply that it should be subject to certain limitations. The correct rule as to the admission of skiagraphs was enunciated in the first district court of Colorado (*Smith vs. Grant*, Chicago Legal News, 1896, xxix, 145) in scarcely more than a year after the announcement of Roentgen's discovery. The court used the following language in respect to a radiograph that was offered in evidence:

"These exhibits are only pictures or maps to be used in explanation of a present condition and therefore are secondary evidence and not primary. They may be shown to the jury as illustrating or making clear the testimony of experts."

A few years later the Massachusetts Supreme Court reversed a case because of the failure of the trial court to admit an x-ray negative in evidence. In commenting upon the exclusion of these pictures at the trial the court said:

"While a picture produced by an x-ray cannot be verified as a true representation of the subject in the same way that a picture made by a camera can be, yet it should be admitted if properly taken."

The untoward action of the x-ray upon the skin is dependent upon several factors:

1. The distance of the skin from the anode or target of the tube.
2. The spark gap or voltage. This may be read directly from a voltmeter, the latter being frequently checked by the spark gap.
3. The amperage or current through the tube.
4. Time of exposure.
5. Action of filter.

The effect of the x-ray on the skin varies according to the time of exposure; that is, other things remaining the same, the effect is twice as much if the exposure is two minutes as it would be if the exposure was for one minute. The effect of the x-ray on the skin also varies directly according to the quantity or number of milliamperes passing through the tube; other things remaining the same 10 ma. produce twice the effect produced by 5 ma. Three ma. for four minutes will

have practically the same effect as 4 ma. for three minutes; that is, 12 ma. minutes.

As there is no very accurate method of standardizing the dosage of the *x*-rays, terms have been employed which express the effect upon the skin. An **erythema dose** represents a unit of quantity that in an average person will produce a slight redness of the skin and will ordinarily cause the hair to fall out in three weeks and not be restored in six months. A **skin unit dose** is that quantity which will cause the hair to fall out, but will not cause a redness of the skin. An **intensive dose** will provoke a mild inflammation or erythema of a superficial character in a normal sensitive skin. A **hyperintensive dose** produces a pronounced erythema or a mild second degree inflammation of the normal skin. A **subintensive dose** is three-fourths of an erythema dose. A **semi-intensive dose** is one-half of the erythema dose, while a **fractional dose** is one-fourth, and a **subfractional dose** is one-eighth or one-sixteenth of the erythema dose.

Formulæ have been proposed for determining the element of time with a certain spark gap milliamperage and at a certain distance, but they have not received universal acceptance. Regardless of the manner of estimating dosage, it is to be kept in mind that with all forms of measurements estimates are made of the intensity on the surface of the part irradiated. At this writing there is no accepted standard of estimating the intensity of radiation at a given depth, nor have any absolute standard formulæ for estimating time been developed. The present day estimates are but approximations and in attempting to estimate the degree of intensity at given depths the loss by distance and by absorption must be estimated.

There is a cumulative effect of the *x*-rays. The tissues lose about 50 per cent. of the effect of a single dose in three and a half days, and there is a decrease of about 3 per cent. per day until at the end of seventeen days the effect of the previous dose has been lost.

When the Roentgen rays were first introduced in medicine it was necessary in order to get a shadow of the bones to expose the parts for a considerable period of time, hence in the early days numerous burns were produced in taking skiagraphs. In that early day it was not known that the *x*-ray would produce burns, but this was soon discovered and many of the early operators lost their lives because they did not protect themselves from the action of the rays. With improved technic and the short exposures with which satisfactory plates can be produced, *x*-ray burns have become comparatively rare. The most frequent are those due to the employment of the *x*-ray in treatment. A method of diagnosis, which has, however, resulted in severe burns, is fluoroscopy in its application to abdominal diagnosis, where the operator, using a fluorescent screen, watches the progress of some opaque substance through the alimentary tract. The application of this method necessarily involves a more prolonged exposure than that necessary for taking a picture. As noted above, the term burn does not correctly describe the action of the *x*-ray on the skin; at least if the term burn is

restricted to the application of heat. They are like sunburns, the effects of radiant energy. A sunburn is not followed by immediate vesiculation, but an appreciable interval elapses before the erythema and the formation of blebs. The same is true of the x-ray burn, but commonly the time that elapses between the exposure and the development of the dermatitis is much longer, varying from a day or two to two weeks. The sun's rays cause only a superficial inflammation of the skin, but the destructive effect of the x-ray may be much deeper, often followed by ulceration, gangrene, and ultimate exhaustion. Severe pain in the irradiated area is often complained of.

The first case to be adjudicated in America involving an injury from the use of an x-ray was decided January 8, 1904. The opinion was handed down in *Henslin vs. Wheaton* 97 N. W. 882. It was claimed by the plaintiff that Dr. Wheaton had exposed his chest for thirty or forty minutes and that the tube was placed within 2 inches of his body. It was held that no more was demanded of the physician than the exercise of such reasonable care and skill as is usually given by physicians and surgeons in good standing. The rule is one of ordinary care and prudence. In this case the plaintiff offered the testimony of a Professor Freeman, not a medical man, but who stated he was conversant with the use of the x-ray and the trial court excluded his testimony on the ground that not being a medical man he was not qualified to pass on the propriety of the treatment or the use of the x-ray as employed by the defendant. The higher court held that the defendant's objection would have been well taken if the purpose for which the x-rays were employed had been for treatment, but as they were merely for diagnostic purposes the testimony of any person conversant with the use of the x-ray was competent. In the course of its opinion the court recognized, without deciding, that some persons are more susceptible to the rays than others even though the same technic be followed, holding that such, if urged as a defense, becomes a question of fact for the jury.

The next case was that of *Shockley vs. Tucker*, 103 N. W. 360 decided May 5, 1905. This was a case of appendicitis treated by the x-ray in which it was contended by the plaintiff that the treatment was improper and that the x-ray was not adapted for such a purpose. The defendant's counsel argued that whether such treatment was proper must be tested by the rule of the defendant's school. The supreme court in answer to this said that it could hardly be contended that burning was a proper treatment for any disease or in accordance with the theories of any school, and they held that the fact that plaintiff was severely burned was some evidence in itself that the treatment was improper.

Then follows a long line of decisions, some 23 in number, down to and including December, 1921. An examination of these cases shows what might have been expected. Some have taken the view that the x-ray machine was a potentially dangerous instrument and, if an x-ray burn resulted from its application, a presumption at least was raised that it was improperly used, and the operator must show affirma-

tively that he possessed a high degree of skill and had exercised an extraordinary degree of care and diligence in its application. About an equal number of decisions hold that a physician or roentgenologist, or anyone who operates an x-ray machine for any purpose is bound to possess and to use such ordinary and average degree of care and skill as is ordinarily possessed and exercised by members in like communities making use of such x-ray machines. In all cases it is held that one who claims to use the x-ray as a specialty is held to have the skill and to exercise that degree of care common to specialists of this sort. The apparent conflict in these cases grows out of the determination as to whether or not the legal maxim of *res ipsa loquitur* applies. The courts are not in accord in their opinions as to whether or not a burn standing alone and of itself is evidence of negligence in the application or use of the x-ray.

It is difficult to see just how the courts have arrived at the conclusion that an x-ray burn is in itself evidence of negligence. A physician charged with malpractice enters the trial with the presumption that he has discharged his full duty toward his patient. In order to convict him of malpractice it is necessary for the plaintiff to have the testimony of experts to the effect that what the defendant did or omitted to do was not in accordance with proper medical practice. The physician, in the absence of an agreement to that end, is not held to be a warrantor of cure. Therefore, whatever the result following the treatment, the plaintiff by expert evidence must show some act of omission or commission on the part of the defendant that produced the result complained of. Why a distinction is drawn in an x-ray burn case is not made clear by the opinions that so hold. The decisions that hold that the burn itself is an evidence of negligence eliminates other causes that can be directly responsible for the burn. It has been proven that no two individuals are alike in their susceptibility to the x-rays and there is no means of determining before exposing the patient whether or not he is especially susceptible to their action. The measurement of the quantity of the x-ray by photographic strips or pastilles is admittedly subject to considerable error, but granting a reasonable degree of accuracy if they are employed, they would have no value in determining the susceptibility of the patient, as the dose is deposited in the tissues at the time the measurement was being developed. There are many factors that must be taken into consideration which vary the susceptibility. It is known that brunettes react less than blondes. The least sensitive part of the body is the scalp. The face is more sensitive and the thin skin over the sensory surface of the body reacts more readily than the skin in the immediate vicinity. The mucous membranes are probably more sensitive than the normal skin. One of the earliest cases to recognize idiosyncrasy is that of *Bogle vs. Winslow*, 5 Phila. Reports, 136. In this instance the action of chloroform was at issue and the judge instructed the jury that chloroform could produce very different effects in different individuals and it would not be just to make the defendant answerable for conse-

quences which he could not foresee and which were not the ordinary or probable results of what he did. He was only bound to look to what was natural and probable and to what might reasonably be anticipated.

The application of certain chemicals to the skin increases the susceptibility to the action of the rays. It makes no difference whether these are applied before or after the irradiation. The length of time that the skin may remain hypersensitive to the action of the x-rays varies with the strength of the topical applications. Usually the skin will react normally to Roentgen rays one month after topical applications have been discontinued, providing they have not produced a severe reaction. Where such remedies have produced positive inflammation or ulceration, the skin is likely to remain hypersensitive for at least a month after the healing (*Jour. Amer. Med. Assoc.*, November 5, 1921, p. 1489). After an irradiation there may be an itching sensation, to relieve which the patient applies some lotion, which is followed by an x-ray dermatitis which would not have occurred had the lotion not been used. The decision, therefore, that makes the burn itself evidence of negligence eliminates these considerations and imposes liability for results over which the roentgenologist has no control.

Notwithstanding the efforts to arrive at precision in the operation of x-ray machines, there is still much fluctuation in the current which cannot be prevented or controlled. The line voltage is subject to serious variations which alter the tube current. Before exposure the voltage to be employed is determined for the particular treatment. While the treatment is in progress this voltage may be increased, thus altering the quantity and penetration of the current. The fact that the voltage is not uniform plays an important part in the character of the rays and since these fluctuations cannot be prevented the roentgenologist should not be held accountable for damages that may possibly be due to conditions over which he has no control.

In medicolegal jurisprudence a great variety of cases involving almost every kind and character of medical practice may be found. In at least 95 per cent. of these cases none are found in which the result following medical treatment is held to be sufficient within itself to convict the medical man of malpractice. The courts have repeatedly recognized that medicine and surgery are not exact sciences and that the physician or surgeon did not act along mathematical lines but was dependent for success upon the teachings of his science. They give full value to all possible sources of innocent error and realize the limitations of human power. As a result they promulgated the rule that results, howsoever bad, were not to be considered as evidence, slight or otherwise, of negligence, carelessness, or unskillfulness. They further imposed the obligation upon one claiming damages as a result of omission or commission to prove the charges and they have detailed the method by which such proof should be introduced. It is, therefore, difficult to see by what process of reasoning the x-ray should be ex-

cepted from this general universal rule, as this method of diagnosis and treatment has become an established procedure in the practice of medicine. Courts have gone so far as to impose a liability upon physicians for failure to use the x-ray in the diagnosis or treatment of certain cases.

RADIUM

At the present time there have been no adjudicated cases of malpractice involving the use of radium, nor is there any reference to it in text-books on medicolegal relations. A number of suits have been instituted for radium burns, but none of them have been passed upon by courts of appeal. In most of these suits it is alleged that the defendant did not know the quantity or quality of the emanations of the radium which he employed. Many of them also charge the negligent use of radium capsules or radium applicators. In one case in Illinois a radium applicator was applied to a patient's tongue in the treatment of carcinoma. In some manner the capsule became loosened and was swallowed by the patient. It was removed by a surgical operation.

ULTRAVIOLET RAYS

These rays are capable of causing very severe burns, but up to the time of this writing no case has reached a court of appeal in which negligence has been alleged in the application of the violet rays. There is a similarity between an ordinary sunburn and that produced by the ultraviolet rays, though it is possible that the latter may have a much deeper effect if the application is prolonged. To Finsen belongs the credit of having first demonstrated the therapeutic possibilities of actinic light. The original installations of Finsen were cumbersome and they have been practically succeeded by various devices known as the Kromayer and Alpine lamps. They are produced by passing an electric current through a vacuum-tube, which if composed of glass does not permit the ultraviolet rays to pass. If on the contrary, fused quartz be used, as in the Kromayer lamp, the ultraviolet rays are not intercepted. The heat rays are intercepted in the Kromayer lamp by a continuous flow of cold water. Such a lamp may be pressed against the skin and will feel distinctly cold and at the same time it will cause a severe burn in less than a minute.

THE COMMON LAW AND STATUTORY OBLIGATIONS OF PHARMACISTS

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I. THE COMMON LAW OBLIGATIONS OF PHARMACISTS

THE common law obligations of pharmacists are those which, in virtue of their special occupation, they owe to their patrons, as determined by the rules of common law, which last may for the present purpose be defined as the "body of rules and principles to be found in the decisions of the highest courts, and in the text-books published by numerous able writers."

These obligations are enforced by civil suits for damages instituted by or in behalf of the parties claiming to be damaged by some alleged neglect of duty on the part of the pharmacist or his agent.

Degree of Skill and Diligence Required of Pharmacists.—In general it may be said that every dealer is under obligation to possess and exercise reasonable or ordinary care and skill in the practice of his occupation, but in this connection the term "ordinary" must be understood as implying a degree of care and skill commensurate with the degree of hazard involved. What might be the exercise of ordinary care in the handling of common groceries might be deemed gross negligence in the handling of drugs and medicines dangerous to human life when incautiously dispensed.

A fair rendering of the decisions of the highest courts upon this point justifies the conclusion that in the handling of dangerous drugs and medicines the pharmacist is required to exercise a high degree of care, and that the failure to employ any necessary precautionary measure therein amounts to gross negligence. Thus in an instructive case (*Howe vs. Rose* 42 N. E., 304) it was held that:

"In view of the dire consequences that may result from the least inattention or want of due care or skill, druggists, apothecaries, and all persons engaged in manufacturing, compounding, or vending drugs and medicines should not only be required to be skilful, but should also be exceedingly cautious and prudent. All persons who deal with deadly poisons, noxious and dangerous substances, are held to a strict accountability. The highest degree of care known to practical men must be used to prevent injury from the use of drugs and poisons. It is for these reasons that a druggist is held to a special degree of responsibility. The care required must be commensurate with the danger involved. The skill employed must correspond with that superior knowledge of the business which the law requires."

In another important case (*Norton vs. Booth*, 34 La. Ann, 913) the plaintiff sued to recover damages for the death of a daughter alleged to

have been caused by the taking of zinc sulphate dispensed by the druggist on an order for Epsom salt. The court said:

"In the discharge of their functions, druggists and apothecaries, persons dealing in drugs and medicines, should be required not only to be skilful, but also exceedingly cautious and prudent, in view of the terrific consequences which may attend, as they have not infrequently in the past, the least inattention on their part. . . . All persons who deal with deadly poisons are held to a strict accountability for their use. The highest degree of care known among practical men must be used to prevent injury from the use of such poisons. A druggist is undoubtedly held to a special degree of responsibility for the erroneous use of poisons, corresponding with his superior knowledge of the business."

Pharmacists Responsible for Negligence or Incompetency of Clerks.—The general rule of law that a principal will be held responsible for the acts of his agents when within the scope of his employment has generally been held to apply to pharmacists and to make them responsible for damages caused by the negligence or incompetency of their assistants.

In a leading case (*Fleet vs. Hollenkemp*, 56 Am. Dec., 568) a clerk, in compounding a prescription calling for equal parts of powdered snake-root and Peruvian bark, negligently powdered the drugs in an uncleaned mill previously used for the grinding of cantharides, whereby a portion of the latter drug was included in the mixture, in consequence of which the patient taking the medicine was injured. The firm was held responsible for the negligence of the assistant. The court said:

" . . . if the defendants, or any employee of theirs in their drug store, in filling such prescription, whether ignorantly or by design, whether with or without the knowledge of the defendants, they being the proprietors, did intermix the poisonous drug cantharides, or Spanish flies, with the bark and snakeroot, and if, in taking this preparation or mixture as medicine, the plaintiff was injured, the defendants, being owners of the drug store, are legally responsible in damages to the plaintiff for the accident, if it was one, and for the outrage, if it was designed."

In an Ohio case (*Davis vs. Guarnieri*, 45 Ohio St., 470) a druggist's clerk delivered a bottle containing bitter oil of almonds with the label "Sweet Oil of Almond." The plaintiff's wife, on taking the liquid, was killed, and the clerk's employer was held liable in damages. The Supreme Court in passing upon the case said:

"A dealer in drugs and medicines who carelessly labels a deadly poison as a harmless medicine and sends it so labeled into the market is liable to all persons who, without fault on their part, are injured by using it as such medicine in consequence of the false label. . . . Where such act is done by an agent, the principal is liable for the injury caused thereby."

Responsibility of Pharmacists to Third Parties.—The responsibility of a pharmacist for failure to exercise a proper degree of care and skill in the conduct of his business may extend beyond the person to whom a drug is sold, and render him liable in damages to a third person who may be injured in consequence of such want of care and skill. The doctrine seems to be that the pharmacist will be liable to the third party when the injury can be regarded as a natural consequence of the

negligence charged, that is, a consequence that could reasonably be expected in the usual course of events. For example, in a leading case (*Thomas vs. Winchester*, 6 N. Y., 397) the evidence showed that the defendant, who was a manufacturer of vegetable extracts, sold to a druggist by the name of Aspinwall, a jar of extract labeled "Extract of Dandelion," but which in fact contained extract of belladonna. The druggist Aspinwall sold the jar to another druggist, Dr. Foord, who in turn sold a portion of it as extract of dandelion to Thomas, whose wife taking the same was injured thereby. Suit was brought for damages against Winchester, the original manufacturer, who sought to defend the action upon the ground that he had not sold the extract to Thomas, and therefore that there was no privity of contract between himself and the plaintiff. The defendant Winchester was held liable, however, the court saying:

"The defendant's duty arose out of the nature of his business and the danger to others incident to its mismanagement. Nothing but mischief like that which actually happened could have been expected from sending the poison falsely labeled into the market, and the defendant is justly responsible for the probable consequences of the act.

The duty of exercising caution in this respect did not arise out of the defendant's contract of sale to Aspinwall. The wrong done by the defendant was in putting the poison, mislabeled, into the hands of Aspinwall, as an article to be sold and afterward to be used as the extract of dandelion by some person then unknown."

In commenting upon this case the Supreme Court of Massachusetts, (*McDonald vs. Snelling*, 14 Allen, 290) has said:

"Here the dealer owed to the public a duty not to expose human life to danger by falsely labeling a noxious drug and selling it in the market as a harmless article. To do so was culpable and actionable negligence toward all likely to be, and who were in fact, injured by the mistake. Any injury that did follow was the natural and easily foreseen result of the carelessness."

So also in the case of *Davis vs. Guarnieri* (45 Ohio St., 470) it was held that:

"A dealer in drugs and medicines who carelessly labels a deadly poison as a harmless medicine and sends it so labeled into the market, is liable to all persons who, without fault on their part, are injured by using it as such medicine in consequence of the false label. The liability of the dealer in such case arises not out of any contract or direct privity between him and the person injured, but out of the duty which the law imposes upon him to avoid acts in their nature dangerous to others."

In the case of *Norton vs. Sewell* (106 Mass., 143) the evidence showed that one Patten had asked the assistant of the apothecary, Sewell, for 2 ounces of tincture of rhubarb, but received instead 2 ounces of laudanum, and that he proceeded to the house of the plaintiff and administered to the plaintiff's husband, Norton, 1 ounce of the liquid in consequence of which he died.

The defendant, Sewell, sought to evade liability for the death upon the ground "that there was no privity of contract between the defendant and the deceased." The court held in favor of the plaintiff and said:

"This finding includes a violation of duty on the part of the defendant, and an injury resulting therefrom to the intestate, for which the defendant was responsible without regard to the question of privity of contract between them."

Responsibility of Pharmacists for Quality of Goods Delivered.

—In general it may be said that the drugs and medicines sold by the pharmacist must be of the kind and quality ordered, or of the kind and quality they are represented to be.

In the sales of ordinary articles of merchandise, especially in the case of articles open to inspection by the purchaser, the common law maxim of *caveat emptor*, "let the purchaser take care," usually applies, that is, the purchaser should see to it that the thing he purchases is the thing he desires. In the case of drugs and medicines, however, the courts seem to hold the seller to a much stricter responsibility.

In passing upon this point one court (*Fleet vs. Hollenkemp*, 56 Am. Dec., 563) has said:

"As applicable to the owners of drug stores, or persons engaged in vending dangerous medicines by retail, the legal maxim should be reversed. Instead of 'caveat emptor' it should be 'caveat venditor.' That is to say, let him be certain that he does not sell to a purchaser or send to a patient, one drug for another, as arsenic for calomel, cantharides for, or mixed with, snakeroot and Peruvian bark, or even one innocent drug in place of another sent for, and designed to produce a different effect.

"It is his duty to know the properties of drugs, and to be able to distinguish them from each other. It is his duty to so qualify himself, or to employ those who are so qualified, to attend to the business of compounding and vending medicines and drugs, as that one drug may not be sold for another; and so that when a prescription is presented to be made up, the proper medicines, and none other, be used in mixing and compounding it."

In a Texas case (*Jones vs. George*, 56 Tex., 149; 42 Am. Rep., 869), where Paris green was ordered for the purpose of killing worms on cotton plants, the druggist by mistake supplied a different substance incapable of destroying worms, in consequence of which the cotton crop was lost or greatly damaged. Here the druggist was held liable. In its decision the court said:

"As a general rule the doctrine [*caveat emptor*] does apply in the purchase of chattels, when an opportunity for examination by the purchaser is shown. But when, from the nature of the article, or the peculiar character of the business in which the same is being sold, it is shown that an examination would not avail the purchaser anything, it might constitute an exception to the general rule, dependent upon the circumstances of each particular case. The appellee was engaged in the business of a druggist, holding himself out to the public as one having the peculiar learning and skill necessary to a safe and proper conducting of the business. The general customer is not supposed to be skilled in the matter, and, as represented in this case, does not know one drug from another; but in the purchase of drugs, the purchaser must rely upon the druggist to furnish the article called for; and in this particular business, the customer who has not the experience and learning necessary to a proper vending of drugs would not be held to the rule that they must examine for themselves. It would be but idle mockery for the customer to make the examination, when it would avail him nothing. On the contrary, the business is such that in the very nature of things the druggist must be held to warrant that he will deliver the drug called for and purchased by the customer."

Proof of Negligence Necessary to Justify Recovery from Pharmacist.—From a study of the circumstances involved in the

preceding cases it will have been observed that in every instance some degree of negligence has been charged to the pharmacist or his agent. In some cases courts have been inclined to hold, or to intimate, that the pharmacist is an insurer of his drugs to the extent of making him liable for damages resulting therefrom whether he is chargeable with negligence or not. The better doctrine, however, seems to be that proof of negligence is essential to sustain the right of a plaintiff to recover damages, *i. e.*, that the defendant must be chargeable with failure to exercise the degree of skill and diligence which the circumstances of the particular case called for.

Thus in a Michigan case (*Brown vs. Marshall*, 47 Mich., 576; 41 Am. Rep., 728) the instruction to the jury by the trial judge warranted the inference that the pharmacist was an insurer of the drugs sold by him, to the extent of making him liable for damages, irrespective of the question of negligence. The Appeal Court held such instruction to be an error, and in ordering a new trial said:

"In this instruction there is no hint of negligence as a necessary element in the right of action. . . .

"That such an error might occur, without fault on the part of the druggist or his clerks, is readily supposable. He may have bought his drugs from a reputable dealer in whose warehouse they have been tampered with for the purpose of mischief. It is easy to suggest accidents after they came into his own possession, or wrong by others of which he would be ignorant, and against which a high degree of care would not have given perfect protection. . . .

"The case, it must be conceded, is one in which a high degree of care may be justly required. People trust not merely their health, but their lives, to the knowledge, care, and prudence of druggists, and, in many cases, a slight want of care is liable to prove fatal to some one. It is therefore proper and reasonable that the care required shall be proportioned to the danger involved. But we do not find that the authorities have gone so far as to dispense with actual negligence as a necessary element in the liability when a mistake has occurred."

Similarly in a New York case (*Allen vs. State S. S. Co.*, 132, N. Y., 95), where injury was alleged to have occurred through the giving of calomel instead of quinin, the court held that:

"A person is not legally responsible for any unintentional injury from a lawful act when the failure to exercise due care cannot be imputed to him. And the burden of proving such lack of care, when the act is lawful, is upon the plaintiff."

Usually the existence of negligence is a question of fact for the jury to determine, but if the facts in the case are not disputed the court may be warranted in directing a verdict against or in favor of the defendant. If the verdict should be against the defendant it would be the part of the jury to assess the amount of damages to be recovered.

Pharmacist Not Responsible for Quality of Proprietary Medicines.—In supplying proprietary medicines of secret composition, such as patent medicines, the pharmacist's responsibility apparently does not extend beyond the duty to deliver the particular article called for. Thus in a Pennsylvania case (*West vs. Emanuel*, 198 Pa. St., 180), where a druggist was sued for damages alleged to have resulted from the taking of a proprietary headache powder sold by him, it was held that:

"In the sale of patent or proprietary medicines furnished by the compounder of the ingredients which compose them, the druggist is not required to analyze the contents of each bottle or package he receives. If he delivers to the consumer the article called for with the label of the proprietor or patentee upon it, he cannot be justly charged with negligence in regard to it."

If the label upon the package of a proprietary medicine should show the presence of a potent drug in amount likely to cause injury when the medicine is used in the manner directed, there is possibility that the pharmacist's responsibility might be affected thereby, but this question does not seem to have as yet been passed upon by our courts.

Effect of Recommendation Upon Pharmacists' Responsibility.—Pharmacists are frequently called upon by their patrons for advice as to the value or suitability of certain compounds or proprietary preparations for various uses. In a Georgia case (*Ray vs. Burbank*, 34 Am. Rep., 103), a pharmacist was asked for a remedy for a horse. He replied, stating that a party of his acquaintance had used a certain mixture in a similar case with success, and recommended it to the plaintiff. He made no charge for the advice, but did charge for filling the prescription. Injury resulting from the use of the medicine, the pharmacist was sued for damages. In holding that the pharmacist was not liable for the injury, the court said:

"At all events, the owner of a horse is entitled to choose his medicine, and, if he chooses it on the mere recommendation of a druggist, and the druggist is guilty of no bad faith, the failure of the medicine is simply a misfortune. The evidence is not necessarily convincing that there was want of skill in the act of compounding or any departure from the recipe either in selecting or combining the materials. All that can be certainly said is, that in the given case, the remedy proved disastrous."

Notwithstanding the above decision it will be wise for the pharmacist to avoid the direct and unqualified recommendation of a preparation unless he is prepared to stand by his statements. Qualified recommendations, as, that he has known the preparation to be used with good success in similar cases, or that many people who have used the preparation think well of it, etc., would probably not be held to constitute such a warranty as to make the pharmacist liable.

In an English case (*George vs. Skivington*, L. R. 5, Exch. 1) a chemist recommended to a customer a chemical compound as a hair wash, stating that it would not injure the person using it. The user being injured thereby, a verdict against the seller for damages was sustained.

It will be observed that this case differed from the Texas case cited in that the chemist stated that the preparation was harmless and would not cause injury to the user. This amounted to the direct assertion of a material fact, which was false, and was not a mere expression of personal opinion.

When Recommendation Constitutes Practice of Medicine.—Pharmacists should beware that in recommending medicinal preparations they do not infringe upon the medical practice acts which restrict the practice of medicine to legally qualified physicians.

In a Kansas case (*Underwood vs. Scott*, 43 Kas., 714; 23 Pac., 942), it was held that the practice of medicine consists in three things:

"First, in judging the nature, character, and symptoms of the disease; second, in determining the proper remedy for the disease; third, in giving or prescribing the application of the remedy to the disease. If the person who makes a diagnosis of a case also gives the medicine to the patient, he is, in our judgment, practicing medicine within the provisions of the statute in question."

It follows from this that if a customer should state his symptoms to a pharmacist and the latter should prepare and sell him a mixture to remove the symptoms he would to all intents and purposes be practicing medicine, and liable accordingly, even though there was no intent in his mind to violate the law.

If a diagnosis is made, the offense will be complete, even though a proprietary remedy is prescribed, but:

"A vender of patent medicines who does not pretend to diagnose and determine which of the remedies is proper in a particular case, is not a violator of this statute."

One who, not being licensed as a physician, should diagnose a case and prescribe a remedy, would be subject to three distinct disabilities: he would be liable to penalties for violation of the medical practice act; he would not be entitled either to enforce payment for the advice given or to recover the price of the medicine furnished; and he would be liable in damages for any injury resulting to the person prescribed for.

On the other hand, if the dealer entirely refrains from passing upon the symptoms presented, and goes no farther than to say that he has known a particular remedy to have been of service in cases where similar symptoms have been present, or that persons with similar symptoms have used a particular remedy with good effect, leaving to the customer the entire responsibility of making the selection, he probably would not be liable.

Effect of Contributory Negligence.—According to the doctrine of contributory negligence as laid down by the courts, a plaintiff, because of some negligent act of his own, may be unable to recover in a suit for damages resulting from the negligence of the pharmacist.

It has been said judicially (*Little vs. Hackett*, 116 U. S., 371), that:

"If the complainant's fault, whether of omission or commission, has been the proximate cause of his injury, he is without remedy against one also in the wrong."

An application of the doctrine of contributory negligence to injuries arising out of the practice of pharmacy is given in the case of *Gwynn vs. Duffield* (61 Iowa, 64).

In this case the plaintiff went into the defendant's store and asked for some extract of dandelion. One of the defendants by mistake took down a jar of belladonna extract and proceeded to fill the order therefrom. While the jar was upon the counter the plaintiff, without invitation, helped himself to a liberal dose of the extract, in consequence of which he was injured. It appears that the injury was caused

by the dose to which the plaintiff had helped himself, and not by the portion weighed out by the defendant. It was held upon this showing of facts that the plaintiff was not entitled to recover, since his own act was the proximate cause of the injury, even though the defendant was also guilty of negligence.

Liability for Sale of Poisons Not Properly Labeled.—In several of the cases previously mentioned poisonous drugs have been dispensed under the labels of harmless ones, either through accident or through some other form of misadventure. Other cases have occurred where pharmacists have sent out dangerous substances, either without any label whatsoever, or with a label not giving sufficient notice of the dangerous character of the drug.

In *Fisher vs. Galloday* (38 Missouri App., 540), a customer sent to a drug store for sulphuric ether and received an unlabeled bottle which he presumed to be the substance ordered but which turned out to be sulphuric acid, from the use of which injury resulted. In passing upon this case the Court of Appeals said:

“Defendant’s furnishing the unlabeled acid was the same, under the circumstances, as if he had labeled it the drug sent for, and, though defendant’s testimony is that acid was called for, yet he did not so label it. If he had observed the dictates of the most ordinary prudence, to say nothing of the law, and labeled the drug, the plaintiff would have discovered the mistake.”

In a New York case (*Wohlfahrt vs. Beckert*, 92 N. Y., 490), the plaintiff’s husband asked the defendant’s clerk for “black drops,” apparently having confused the name with that of “black draught,” a comparatively harmless preparation. The clerk supplied black drop in a bottle labeled simply “Black Drops,” but without the poison label required by statute, though he informed the purchaser verbally that the liquid was a poison, and that he should not take more than 10 or 12 drops at a dose. Notwithstanding this warning, the purchaser took a very much larger dose which caused his death. It was held in this case that the question of the negligence of the druggist was a question of fact for the jury.

In an Indiana case (*Howe vs. Davis*, 42 N. E., 303) it was held that evidence that a druggist who purchased of a wholesale dealer a package of tartaric acid labeled “Rochelle Salts,” and sold a portion of it for Rochelle salts from which injury resulted, was not sufficient proof of negligence to justify recovery.

Effect of Knowledge of Intended Unlawful Use of Drug.—Where a pharmacist has knowledge of an intended unlawful use of a drug furnished by him, the effect is to make him liable for the consequences of such unlawful use of the drug. For example, a druggist who, at the request of a customer, placed croton oil on candy, having reason to believe that the candy was to be administered to a third person for the purpose of annoying him and not for a medicine, was held guilty of assault and battery (*State vs. Monroe*, 121 N. C., 677). Undoubtedly, in such a case the druggist must be regarded as having intended

the injury which was the natural result of his action and must be held liable accordingly. The same would be true if the druggist should sell a drug which he had reason to believe was intended to be used for the purpose of producing abortion.

Liability for Injury Caused by Prescription.—It sometimes occurs that a druggist is called upon to fill a physician's prescription which he has reason to believe will be dangerous, or even deadly to the patient if used in the manner directed. If the physician cannot be reached, or if he insists that the prescription is correct, the only way to avoid responsibility is to refuse to fill the prescription. If compounded as written and injury resulted in consequence, the compounder would be liable as well as the physician. (Hilliard on Torts, 297).

In a Philadelphia case (*Commonwealth vs. Bauer, Oyer, and Terminer*, April, 1869) the judge said:

"If the exercise of reasonable care would have warned him that he [the druggist] was preparing something which would inevitably kill, it would be criminal for him to go on."

In the case of *Tarlton vs. Lagarde* (46 La. Ann, 1368) it has been held that the druggist may refuse to fill a physician's prescription, without being liable in damages to the physician, provided he avoids the giving of reasons that would be slanderous to the physician. In this case the court said:

"In many cases the druggist may have the best of reasons for declining to fill prescriptions. As a chemist he may perceive or have cause to suspect the physician erred in his prescription, or the druggist may not have at hand the ingredients, or he may distrust his ability to prepare the prescription, or other causes may incline the druggist to undertake filling the prescription presented to him. Recognizing the room for all such cases, we cannot hold that the mere refusal of a druggist to fill prescriptions furnishes any occasion to hold him for damages to the physician who gives the prescription."

II. THE STATUTORY RESPONSIBILITIES OF PHARMACISTS AND THEIR AGENTS

The legal responsibilities of pharmacists and their agents are determined partly by the positive provisions of special statutes specifically imposing certain public duties and obligations, and are partly common law obligations, or the obligations of members of society to each other as defined and determined by the application of general legal principles.

The special statutes referred to are in the nature of police regulations enacted by some competent legislative body, and are represented by the pharmacy acts, the food and drugs acts, and the acts regulating the sale of poisons, habit-forming narcotic drugs, and of alcoholic liquors. As the various state statutes differ so much from each other in their details, it is impossible to present more than a brief outline of their principal provisions, so that it is practically necessary for the pharmacist to provide himself with copies of the various state and federal statutes

to which he is subject, as well as copies of the various regulations issued by the boards and officials charged with their enforcement.¹

Violations of state and federal statutes are prosecuted in the name of the state or federal government, and are punished by the imposition of fines or imprisonment, or both; obligations under the common law are enforced by civil suits for damages instituted by or on behalf of the parties claiming to be injured by the alleged failure of the pharmacist to observe such obligations.

THE STATE PHARMACY ACTS

The pharmacy acts of the several states commonly define what shall constitute the practice of pharmacy, provide methods for the examination and registration of the persons who may legally compound and sell drugs, medicines, and poisons, and create the legal machinery for the administration and enforcement of the law.

While the provisions of the state pharmacy acts have many requirements in common, they differ so much in their details that each pharmacist should be provided with a copy of the special statute of his own state.

The provisions common to all or nearly all of the state pharmacy acts are the following:

1. The Board of Pharmacy.—The act creates a board of administration known variously as the State Board of Pharmacy, Board of Pharmaceutical Examiners, State Pharmaceutical Examining Board, Commissioners of Pharmacy, etc.

The number of members of the board of pharmacy varies, the most common number being five. The members are usually appointed by the governor of the state, the terms being so arranged that the term of one member expires each year. Very commonly the law provides that the state pharmaceutical association may annually present a list of nominees to the governor, from which the latter may select one to fill the annual vacancy on the board.

Usually the expenses of the board of pharmacy are paid from the receipts from examinations and registration, but in a few states the examination and registration fees are paid into the state treasury and the board is maintained by appropriations therefrom.

2. Limiting the Practice of Pharmacy to Persons Specified in the Act.—While there is no uniformity in the language employed, the pharmacy acts usually prohibit the conducting of any retail drug or chemical store, or the compounding or dispensing of medicines or poisons except by persons registered under the act.

The law generally contains a provision excepting from this prohibition the dispensing by physicians to their own patients, and the sale by general dealers of a specified list of common household remedies,

¹ Copies of the state pharmacy and poison laws can usually be obtained by addressing the Secretary of the State Board of Pharmacy at the capital city of the state. Copies of the federal laws and regulations can usually be obtained from the appropriate department at Washington, D. C.

proprietary medicines, and of certain poisons used as insecticides, as Paris green, etc. The exception authorizing a physician to dispense medicines to his own patients does not, however, authorize him to engage in the business of supplying drugs and medicines to persons not under his treatment as patients.

3. Defining the Character of Licenses to Be Issued By the Board.—The principal license granted by the board of pharmacy is known variously as "Pharmacist," "Registered Pharmacist," "Licensed Pharmacist," "Qualified Pharmacist," etc., which entitles the holder to conduct a retail pharmacy or drug store.

Registered pharmacists are usually required to be eighteen years or more of age, to have a certain amount of experience in a pharmacy, usually four years, and to pass a successful examination before the board of pharmacy. In some states they are also required to be graduates of a college of pharmacy before they are admitted to examination.

In many states a second grade of license is provided for, that of "Registered Assistant" or "Qualified Assistant," etc., the holders of which are permitted to sell medicines and poisons and to fill prescriptions under the supervision of a registered pharmacist.

A few states provide for still a third grade of license, or that of "Druggist," the holder of which is permitted to deal in certain kinds of drugs and medicines. Occasionally the law provides for an "Apprentice," who is permitted to render certain limited kinds of service in a drug store.

4. Ownership of Drug Store Not Confined to Registered Pharmacist.—Although only a person licensed as a pharmacist can conduct a pharmacy, it has been held that an unlicensed person can own a drug stock, provided the actual conduct of the business is in charge of a registered pharmacist.

One of the usual requirements of a pharmacy act is that the license of the person in charge of the same shall be kept exposed in a conspicuous position in the place of business.

THE POISON ACTS

The poison acts of the several states differ so widely in their specific requirements that the pharmacist in order to conduct his business legally will find it necessary to familiarize himself with the act of the state in which he does business.

Many statutes do not endeavor to define a poison, but merely give a list of substances which are to be deemed poisons and handled accordingly. A few state laws give a definition of what shall be deemed a poison, as, for example, the poison act of Pennsylvania which defines a poison as "Any drug, chemical, or preparation which according to standard works on medicine or materia medica is liable to be destructive to adult human life in quantities of 60 grains or less."

When the statute does not define a poison the burden is upon the pharmacist to determine what substances should be considered as poisons, and to govern himself accordingly.

The Labeling of Poisons.—While the requirements for the handling of poisons differ greatly in the various statutes, the ones most frequently included are as follows:

The label must bear the word *Poison*, plainly written or printed, a picture of the "death's head" or skull and cross-bones, and the names of two or more readily obtainable antidotes.

Sometimes a special color of ink is prescribed for the label, as red ink on white paper, white ink on red paper, etc.

Other Requirements of the Poison Acts.—Other requirements occasionally appearing in the statutes are:

(a) That the seller must first learn by inquiry that the purchaser is acquainted with the poisonous nature of the substance and desires it for a lawful purpose; (b) That a record of the name and quantity of the poison, the purpose for which it is required, and the name of the purchaser be kept in a suitable record book, etc.

It is also frequently provided that poisons shall not be sold to minors except upon the written order of an adult.

When the statute gives a list of substances to be deemed poisons the list is frequently divided into Schedules A and B, the first containing a list of ordinary poisons which only need to be properly labeled, and the second enumerating the kinds of substances the sale of which must be recorded as described above.

Whether the above requirements are specifically stated in the law or not, it will be good policy for the pharmacist carefully to observe them in his business, namely, to see that every poisonous substance is properly labeled with its name, the word *Poison*, the death's head, and the names of two or more readily obtainable antidotes. If the substance is one likely to be dangerous if used incautiously, the seller should ascertain that the purchaser is aware of its poisonous character, and keep a record of the sale. He should also refuse to sell dangerous substances to children except upon the written order of an adult.

Medicines compounded upon the prescription of a physician should not be labeled poison without the consent of the physician, but if the preparation is one likely to prove injurious if taken internally, it should be labeled "For External Use Only," or with some other statement to indicate that the preparation is not intended for internal use.

The acts regulating the sale of poisons are criminal statutes, and their violation is punishable by fines. The responsibility of pharmacists to third persons for injuries arising out of the sale of poisons is considered in another section of this chapter.

THE ANTINARCOTIC ACTS

Traffic in certain habit-forming narcotic drugs is regulated both by federal and by state statutes.

The state antinarcotic acts differ so widely among themselves that it would not be profitable to attempt to present their various provisions here. The cautious physician or pharmacist will, of course, supply himself with a copy of the act of his own state.

The Federal Antinarcotic Act.—The federal act, commonly known as the "Harrison Law," is in form an act for the raising of revenue, although its real purpose is to regulate the traffic in certain named drugs both in interstate commerce and within state limits.

The drugs and preparations covered by the act are "opium and coca leaves, or any compound, manufacture, salt, derivative, or preparation thereof."

Dealers Must Register and Pay Tax.—Every person who "produces, imports, manufactures, compounds, deals in, dispenses, sells, distributes, or gives away" any of the articles covered by the act must register annually with the Collector of Internal Revenue of the district within which he is located, and pay the tax.

Only the person actually in responsible control of the business is required to register and pay the tax, hence the employee of a registered dealer is not required to register. The exemption from registration applies to officers of the law, and to officers of the Army and Navy in so far as their official duties require them to obtain, possess, and handle the drugs covered by the act.

Any person, whether a doctor or druggist or not, may register and pay the tax, but since it is made unlawful to make use of the official order blank to obtain the named drugs for any other purpose than the conduct of a lawful business or legitimate practice of a profession, it follows that the effect of the law is to restrain the traffic in such drugs to physicians, veterinarians, druggists, wholesale druggists, and manufacturing pharmacists.

Registration and payment of the tax does not entitle the registrant to deal in the named drugs except in the manner provided in the state law. In other words, the dealer is subject to the requirements both of the federal act and the law of the state in which he does business.

The Official Order Blank.—Dealers can obtain the drugs covered by the act only by means of orders written upon a special form of order blank supplied by the Collector of Internal Revenue and issued only to persons registered under the law, which order blanks are serially numbered and must bear the name of the registered dealer to whom they are issued.

Each order must be written in duplicate, one copy being furnished the dealer upon whom the order is given, the other being retained by the dealer giving the order. Both the purchaser and the dealer must preserve their respective copies for a period of two years, subject at all times to inspection by state, municipal, and United States officers of the law.

Order Blanks Not Required in Certain Cases.—The use of the official order blank is dispensed with in the following cases:

1. When the drug is dispensed upon the written prescription of a physician, dentist, or veterinarian registered under the act.

Such prescriptions in order to be valid protection to the dispenser must be in writing, must bear the signature and federal registration number of the writer, and must be dated. Such prescriptions must be

preserved for a period of two years, subject to inspection by proper officers of the state, municipality, and United States.

Such prescriptions may not be refilled; neither is it lawful to fill prescriptions given by telephone or by word of mouth.

2. The official order blank is not required when drugs are dispensed directly to a patient by a physician, dentist, or veterinarian in the "course of his professional practice," but he must keep a record of the drugs thus dispensed, except when dispensed to patients upon whom he personally attends. It is held by the Revenue Department that to "personally attend" means to visit,¹ and, therefore, that drugs dispensed by the physician in his office must be recorded.

3. The official order blank is not required when drugs are sold to dealers in foreign countries in accordance with the law of such countries, and in accordance with the laws of the United States, the reason for this exemption being that it would be impossible for foreign dealers to register as dealers within the United States and obtain the official order blanks.

4. The official order blank is not required for sales to officers of the United States or of state governments, or to officers of departments of the public service, provided, of course, that the said officers are obtaining the drugs for lawful public purposes. The prudent druggist will, of course, take ample precautions to insure that such officers are properly authorized to obtain the drugs.

5. The official order blank is not required for the sale of

(a) Preparations that do not contain more than 2 grains of opium, or $\frac{1}{4}$ grain of morphin, or $\frac{1}{8}$ grain of heroin, or 1 grain of codein, or of any salt or derivative of these, in 1 fluidounce or in 1 avoirdupois ounce.

(b) Liniments, ointments, or other preparations prepared for external use only, *provided* such preparations do not contain cocain, or alpha- or beta-eucain, or synthetic substitutes for the same.

(c) Decocainized coca leaves and preparations made therefrom.

The foregoing exemptions apply only when the various preparations are dispensed *in good faith as medicines*, and not for the purpose of evading the provisions of the law. It follows, therefore, that the furnishing of paregoric to an opium habitué for the purpose of satisfying his craving for opium would render the seller liable to all the penalties of the act.

Burden of Proof Upon Dealer.—It is unlawful for an unregistered person to have possession of any of the inhibited drugs and preparations, and the statute specifies that proof of possession shall be deemed presumptive evidence of violation of the law.

This presumption does not apply to possession by the employee of a registered person acting within the scope of his employment, nor to possession by a patient when obtained under a lawful prescription, nor to possession by a warehouseman or common carrier, nor to possession by an officer of the law in the discharge of his duties.

When exemption is claimed by any person the burden of proof

¹ This ruling of the Treasury Department is considered to be of doubtful validity.

that the possession is innocent is placed by the law upon the person claiming the exemption.

Penalties for Violation.—The penalties for the violation of or for failure to comply with any provision of the federal law are extremely severe, and consist of a fine not to exceed \$2000, or imprisonment not to exceed five years, or both fine and imprisonment, at the discretion of the court.

It should always be borne in mind that physicians and druggists are subject to the provisions both of the federal act and of the special act of the state in which they may be located, and that compliance with one act does not release one from the duty of observing the requirements of the other.

THE FOOD AND DRUGS ACT

The federal food and drugs act, commonly cited as the Food and Drugs Act of June 30, 1906, is an act of Congress regulating the quality and labeling of foods and drugs as transported in interstate commerce, *i. e.*, commerce crossing state or territorial boundaries. Foods and drugs—except alcoholic liquors and certain habit-forming narcotic drugs—when manufactured and sold wholly within the limits of a state are subject exclusively to the provisions of the state law. While most of the state food and drug acts conform in general to the federal act, they differ so greatly in their details as to require reference to the specific act in each state, in order to determine the pharmacist's responsibility thereunder.

Definitions of Foods and Drugs.—In the federal act foods are defined as including "all articles used for food, drink, confectionery, or condiment by man or other animals, whether simple, mixed, or compounded."

Drugs are defined as including "all medicines and preparations recognized in the U. S. Pharmacopœia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals."

Adulteration of Drugs Defined.—In the federal act a drug is adulterated:

First.—If, when "sold under or by a name recognized in the U. S. Pharmacopœia or National Formulary, it differs from the standard of strength, quality, or purity as determined by the test laid down in the U. S. Pharmacopœia or National Formulary at the time of investigation."

Second.—"If its strength or purity fall below the professed standard or quality under which it is sold."

The essence of the above definitions is simply that a drug must be of the quality it is represented to be, *i. e.*, that if it is a drug or compound recognized by the U. S. Pharmacopœia or National Formulary, it must correspond in strength, purity, and quality to the standard specified in these works, or if it is a drug or compound not recognized

by the Pharmacopœia or National Formulary, then it must, in fact, correspond to the standard which its name or label indicates or professes to follow.

According to the first definition of adulteration given above a drug sold by a title recognized in the Pharmacopœia or National Formulary would always have to be of Pharmacopœial or National Formulary quality, which would at times be inconvenient or impossible, since different strengths and qualities are required for different uses. Accordingly, the law provides a qualification of the definition which reads, "Provided, that no drug defined in the U. S. Pharmacopœia or National Formulary shall be deemed to be adulterated under this provision if the standard of strength, quality, or purity be plainly stated on the bottle, box, or other container thereof, although the standard may differ from that determined by the test laid down in the U. S. Pharmacopœia or National Formulary."

This provision, commonly referred to as the "variation clause," consequently permits the sale of U. S. Pharmacopœia and National Formulary substances of qualities to correspond to the purposes for which they are required, provided they are labeled so as plainly to state their quality.

Definition of Misbranding.—The federal statute likewise defines and prohibits the misbranding of foods and drugs.

A drug is deemed to be misbranded:

If the package or label "shall bear any statement, design, or device regarding such article, or the ingredients or substances contained therein which shall be false or misleading in any particular," or "which is falsely branded as to the state, territory, or country in which it is manufactured or produced." A drug is also deemed to be misbranded:

First.—"If it be an imitation of or offered for sale under the name of another article."

Second.—(a) "If the contents of the package as originally put up shall have been removed in whole or in part, and other contents shall have been placed in such package," or

(b) "If the package fail to bear a statement on the label of the quantity or proportion of any alcohol, morphin, opium, cocain, alpha- or beta-eucain, chloroform, cannabis indica, chloral hydrate, acetanilid, or any derivative or preparation of any such substances contained therein."

(This last statement is required in the case of compounds prepared on physicians' prescriptions and preparations recognized in the U. S. Pharmacopœia or National Formulary when they are transported across state or territorial lines, except when they are so transported by either the prescribing physician or by the patient or by a member of the patient's family.)

By an act approved August 23, 1912, commonly known as the Sherley Amendment, the original section of the Food and Drugs Act relating to misbranding was amended by adding the following:

Third.—"If its package or label shall bear or contain any statement, design, or device regarding the therapeutic or curative effect of such an article or any of the ingredients or substances contained therein which is false and fraudulent."

The Guaranty Clause.—"No dealer shall be prosecuted under the act when he can establish a guaranty signed by the wholesaler, jobber, manufacturer, or other person residing within the United States from whom he purchased such article, to the effect that the same is not adulterated or misbranded within the meaning of this act, designating it."

The guaranty to afford protection must contain the name and address of the party or parties making the sale of such article to such dealer, in which case the giver of the guaranty is amenable to the provisions of the act in place of the dealer. The guaranty affords protection to the dealer only when the article is sold in the unbroken original package. If the package has been opened before sale, the dealer and not the guarantor will be liable.

THE FEDERAL PROHIBITION ACT

The Federal Prohibition Act is so lengthy, so complex in its provisions and so far reaching in its effects, and the regulations issued for its interpretation and enforcement so voluminous, that only a bare summary of the principal requirements can be given here. Persons interested in the sale or dispensing of liquids containing alcohol should therefore provide themselves with a copy of the text of the law and of the regulations issued thereon.¹

Intoxicating Liquor Defined and Prohibited.—Any liquid containing $\frac{1}{2}$ of 1 per cent. or more of alcohol by volume, and which is fit for beverage purposes is an intoxicating liquor within the meaning of the law, and its manufacture, sale, transportation, delivery, possession, etc., is prohibited, except as specifically provided in the act.

It follows that a liquor may be an intoxicating liquor legally when not intoxicating in fact, *i. e.*, when it contains $\frac{1}{2}$ per cent. of alcohol and is fit for beverage purposes.

Articles Excepted from the Provisions of the Law.—The following articles, after having been manufactured and ready for the market, are excepted from the provisions of the act:

(a) Denatured alcohol and denatured rum produced and used as provided in the regulations.

(b) Medicinal preparations manufactured in accordance with formulas prescribed by the U. S. Pharmacopœia, National Formulary, or American Institute of Homeopathy, that are unfit for use for beverage purposes.

(c) Patented, patent, and proprietary medicines that are unfit for beverage purposes.

¹ Copies of the law and regulations, comprising considerably more than 200 printed pages, can be obtained from the office of the Federal Prohibition Commissioner, Washington, D. C.

(d) Toilet, medicinal, and antiseptic preparations that are unfit for use for beverage purposes.

(e) Flavoring extracts and syrups that are unfit for use as a beverage or for intoxicating beverage purposes.

(f) Vinegar and preserved sweet cider.

In every case in order to bring the preparation within the preceding exemptions it must be *unfit for beverage purposes*.

A list of U. S. Pharmacopœia and National Formulary preparations considered fit for beverage purposes is published by the Prohibition Unit of the Bureau of Internal Revenue.

When Medicinal Preparations are Regarded as Unfit for Beverage Purposes.—In general, medicinal preparations are regarded by the Prohibition Unit as unfit for beverage purposes when they contain no more alcohol than is necessary for the purposes of extraction, solution or preservation, and contain in each fluidounce a dose as a whole, or in compatible combination, of one or more agents of recognized therapeutic value, and contain no agents either chemically or physiologically incompatible with the active medicinal agents upon which the medicinal claims are based.

Although medicinal preparations of this class may be dealt in without a permit, their manufacture and the handling of the alcohol used therein is subject to all the requirements of the Prohibition Act.

The Prohibition Commissioner is authorized by the law to order a change in the formula of any preparation on the exempted list if he finds that it is being used as a beverage, and if such change in formula is not made, he may refuse permits for the purchase of alcohol to be used in the manufacture of such preparation.

When Traffic in Intoxicating Liquors is Lawful.—The manufacture, sale, purchase, possession, transportation, etc., of intoxicating liquors is lawful only when a permit authorizing the same has been obtained from the Director of Prohibition of the state in which the applicant resides. All such traffic, of course, to be lawful must be for other than beverage purposes.

Permits to manufacture, prescribe, sell, or transport intoxicating liquors may be issued for one year, but permits to purchase such liquors are limited to ninety days from the date of issuance.

Permits to sell liquors at retail can be issued only to a duly licensed pharmacist. Any sale of less than 5 gallons is a sale at retail; a sale of 5 gallons or more is a sale at wholesale.

Permits to prescribe liquor can be issued only to duly licensed physicians actively engaged in the practice of their profession.

The Commissioner in his discretion may require a bond in suitable amount to insure compliance with the provisions of the law before issuing any permit. Such bonds are required in practically all cases. Permits are not required to purchase liquor for medicinal purposes on the prescription of a physician when the prescription complies wholly with the requirements of the law.

Purposes for Which Permits May Be Issued.—Permits for the manufacture, transportation, sale, use, etc., of intoxicating liquors may be issued for the following purposes:

1. For the manufacture of the articles and preparations named in *a, b, c, d, e,* and *f,* of exempted preparations listed above, and in the manufacture of certain other preparations.

2. To retail druggists or pharmacists for the compounding of medicinal preparations unfit for beverage purposes on physicians' prescriptions, and for dispensing upon physicians' prescriptions.

3. To physicians, dentists, and veterinarians for use in their professional practice.

4. To persons conducting hospitals and sanatoriums for medicinal, scientific, and manufacturing purposes.

5. To manufacturing and industrial establishments for first aid treatment. (Potable distilled spirits only.)

6. Alcohol to be used in the manufacture of denatured alcohol and for medication by druggists and pharmacists.

7. For laboratory purposes and in general manufacturing and technical processes.

8. For sacramental purposes or like religious rites.

Wines for Sacramental and Religious Rites.—The manufacture, sale, transportation, importation, possession, or distribution of wine for sacramental purposes or religious rites by persons holding permits for such purposes is lawful, but such wines may not be furnished by the dealer to any person not a rabbi, minister of the gospel, priest, or an officer duly authorized by a church or congregation, and such wines may be dispensed by the rabbi or minister to members of his congregation only. Members of the Jewish faith are entitled to receive not to exceed 10 gallons of wine in one year for the celebration of religious rites in the homes of such families.

The diversion of sacramental wines to any other purposes than those prescribed under the law is prohibited.

The Prescribing of Liquors for Medicinal Purposes.—A duly licensed physician in active practice, holding a permit from the Director of Prohibition, may prescribe alcoholic liquors for medicinal use after careful physical examination of the person for whose use the liquor is intended, or if such examination is impracticable, then upon the best information obtainable, when he believes in good faith that the use of such liquor is necessary and will afford relief from some known ailment.

A physician not holding a permit may not issue prescriptions for intoxicating liquors.

Only spirituous liquors (distilled liquors), or vinous liquors (wines) containing not more than 24 per cent. of alcohol, can be prescribed by a physician, and of these not more than 1 pint of a spirituous liquor or $\frac{1}{4}$ gallon of vinous liquor on one prescription, or for any one person within a period of ten days, and the aggregate of the alcohol contained in the liquors thus purchased must not exceed $\frac{1}{2}$ pint. Ale and beer,

being neither spirituous nor vinous liquors, cannot be lawfully prescribed.

Physicians may not prescribe liquors for their own personal use, nor obtain liquor for their personal use upon their own prescriptions.

All prescriptions for liquor must be upon special printed blanks, consecutively numbered, issued by the Prohibition Commissioner, and no physician may issue more than 100 prescriptions for liquor within a period of ninety days without special permission from the Commissioner.

In emergency, as when necessary to save life, relieve great pain, etc., a physician may use other than the official blank, but the emergency prescription must contain all of the data provided for on the official blank, and a copy must be furnished to the Prohibition Director and a record kept as in other cases.

The official prescription blank is to be used only when unmedicated liquor is prescribed, and must not be used for alcohol-containing medicines which are unfit for beverage purposes.

Accurate copies of all prescriptions issued must be entered upon the stubs attached to the blanks, and these stubs, together with all unused or mutilated blanks, must be returned to the Commissioner.

Physicians issuing prescriptions for intoxicating liquors must keep an accurate record on a form furnished by the Director of Prohibition, showing the date of issue, to whom issued, the kind of liquor, the purpose or ailment for which prescribed, the quantity prescribed, and the amount and frequency of the dose, which record must at all times be open to inspection by officers of the law.

Dispensing of Liquor on Prescriptions.—Prescriptions for medicinal liquors can be dispensed only by duly licensed retail pharmacists holding a dispensing permit. No prescription may be filled more than once, and the pharmacist must indorse upon the prescription, over his own signature, the word "Canceled," and make the canceled prescription a part of the record he is required to keep. Pharmacists must preserve in a separate, carefully guarded file one copy of each prescription filled, and must transmit once a month to the Prohibition Director a list of prescriptions for intoxicating liquors filled by them, showing the names of the prescribing physicians, the names of the patients, and the total quantity of liquor dispensed to each patient during the month.

Pharmacists are required to keep an accurate record of all intoxicating liquors delivered to or received by them, and before the 10th of each month must forward a transcript of such record to the Director of Prohibition, showing all transactions during the preceding month.

Pharmacists dispensing intoxicating liquors on prescriptions are required to pay a retail liquor dealer's tax of \$25.00 yearly, and to keep the special tax certificate conspicuously posted in their place of business.

Physicians, Dentists, and Veterinarians May Obtain Liquors in Certain Cases.—Physicians having permits for such purpose may

obtain not to exceed 6 quarts of intoxicating liquor in any calendar year for administration to their patients for medicinal purposes, where delay in procuring the same through a pharmacist upon a prescription might result in loss of life, aggravation of the ailment, or intense suffering.

Physicians may also obtain liquors for use in the compounding of medicinal preparations used by them, and alcohol for other than internal use.

Dentists and veterinarians holding permits may obtain not to exceed 6 quarts of alcohol in any calendar year for use in their professional practice only.

State Prohibition Laws.—While resembling the Federal Act in their main provisions, the special prohibition acts of the several states differ so much in their details that a worth-while summary would not be profitable.

Since compliance with the Federal Act does not relieve from the necessity of complying with the provisions of the state law, it follows that physicians and pharmacists will, of necessity, provide themselves with a copy of the act and official regulations of the state in which they are located.

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